NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults

Novartis Pharmaceuticals UK Ltd.

Patient access scheme submission template

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1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Gilenya®▼ (fingolimod).

Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.

These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

3.2 Please outline the rationale for developing the patient access scheme.

To provide a cost-effective therapy to the NHS, thereby facilitating access for relapsing multiple sclerosis patients (RRMS). The patient access scheme (PAS) is a mechanism through which the NHS will be able to procure Gilenya at a price lower than list.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The Gilenya PAS is a financially based scheme: simple confidential discount to the list price.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS will apply to all supplies and preparations of Gilenya.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is a simple confidential discount and is not dependent on any criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The patient access scheme will apply to all supplies and preparations of Gilenya.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The NHS Trust signs a commercial agreement with Novartis Pharmaceuticals UK Ltd. The hospital pharmacy then orders Gilenya through the normal procedure. Gilenya is provided to the NHS Trust at list price minus the discount, applied to the invoice.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional information, further to the standard NHS pharmacy procurement procedure, need be collected routinely.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

3.10 Please provide details of the duration of the scheme.

The scheme will be in place until NICE review and subject to Department of Health agreement.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

A draft purchase agreement letter and terms are included in the appendix.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

This is not an outcomes based scheme.

4 Cost effectiveness.

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The population is already included in the submission of evidence for the STA of Gilenya.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Please find attached the economic model with the scheme incorporated. No other changes have been made.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

A simple confidential discount of [redacted] is applied to the list price of Gilenya in the model. This is in sheet 'Treatment Costs' and the user can toggle between applying the PAS or not (Cell I27).

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data is already included in the submission of evidence for the STA of Gilenya

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There are no costs associated with the implementation and operation of the PAS because the discount is applied to the invoice. Table 1 has therefore been removed.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

There are no additional treatment-related costs incurred by implementing the PAS. Table 2 has been removed.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.*

- the results for the intervention without the patient access scheme

In the Novartis submission for Gilenya the results of the base case analysis comparing Gilenya to Avonex (Interferon beta 1a) in Population 1b were reported, these are reproduced in Table 1. The generic names of the beta interferons are very similar. To aid understanding we have used the trade names for the beta interferons throughout this document.

Table 1 Base-case results (without the PAS)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Avonex	271,647	3.98	—	—	—
Gilenya	321,721	4.88	50,084	0.90	55,634

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

- the results for the intervention with the patient access scheme.

When the PAS is applied the cost-per QALY reduces to below both the £20k and £30k threshold; the base case results are shown in Table 2.

Table 2 Base-case results (with the PAS)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Avonex	271,647	3.98	—	—	—
Gilenya	281,404	4.88	9,758	0.90	10,839

* For outcome-based schemes, please see section 5.2.8 in appendix B.

4.8 Please present in separate tables the incremental results as follows. †

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

The incremental base case results are presented in Section 4.7

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The results of the deterministic sensitivity analysis are presented in Table 3 and Figure 1. Please note that the relative risk (RR) of progression for Gilenya and Avonex are not plotted on the tornado diagram because it is not intuitive how to plot the negative ICERs.

† For outcome-based schemes, please see section 5.2.9 in appendix B.

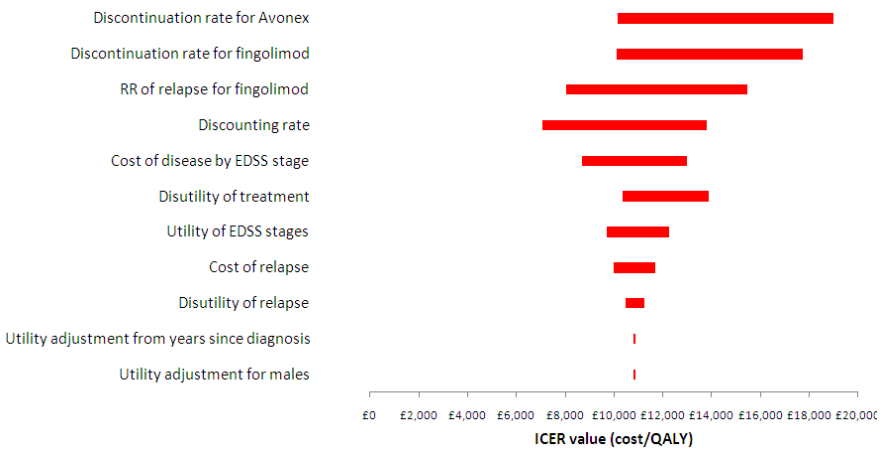
Table 3 Deterministic sensitivity analyses (with PAS)

Parameter		Level	Value	ICER
Efficacy	RR of progression for Gilenya	Lower 95% CI	0.332	£1,092
		Upper 95% CI	1.210	-£41,012 (Gilenya dominated)
	RR of progression for Avonex	Lower 95% CI	0.308	-£30,169 (Gilenya dominated)
		Upper 95% CI	2.404	-£4,772 (Gilenya dominates)
	RR of relapse for Gilenya	Lower 95% CI	0.388	£8,042
		Upper 95% CI	0.805	£15,457
	RR of relapse for Avonex	Lower 95% CI	0.567	£18,058
		Upper 95% CI	1.535	£2,079
	Discontinuation rate for Gilenya	Lower 95% CI	0.0045	£17,730
		Upper 95% CI	0.0342	£10,090
	Discontinuation rate for Avonex	Lower 95% CI	0.0138	£10,159
		Upper 95% CI	0.0545	£18,993
Cost	Cost of relapse	80% of base values	£2,431	£11,700
		120% of base values	£3,647	£9,978
	Cost of disease by EDSS stage	80% of base values	£597 to £16,241	£12,978
		120% of base values	£895 to £24,361	£8,701

Parameter		Level	Value	ICER
Utility	Utility of EDSS stages	80% of base values	RRMS: 0.696 to –0.125 SPMS: 0.660 to –0.161	£12,270
		120% of base values	RRMS: 1 to –0.188 SPMS: 0.990 to –0.241	£9,708
	Utility adjustment from years since diagnosis	Lower 95% CI	0.001	£10,882
		Upper 95% CI	0.003	£10,797
	Utility adjustment for males	Lower 95% CI	–0.007	£10,849
		Upper 95% CI	0.041	£10,830
	Disutility of relapse	Lower 95% CI	–0.096	£10,469
		Upper 95% CI	–0.046	£11,237
	Disutility of treatment	80% of base values	–0.0079 to –0.0383	£13,883
		120% of base values	–0.01188 to –0.05742	£10,346
	Discounting rate	Lowest value	0%	£7,066
		Highest value	6%	£13,781

CI, confidence interval; EDSS, Expanded Disability Status Scale; RR, relative risk.

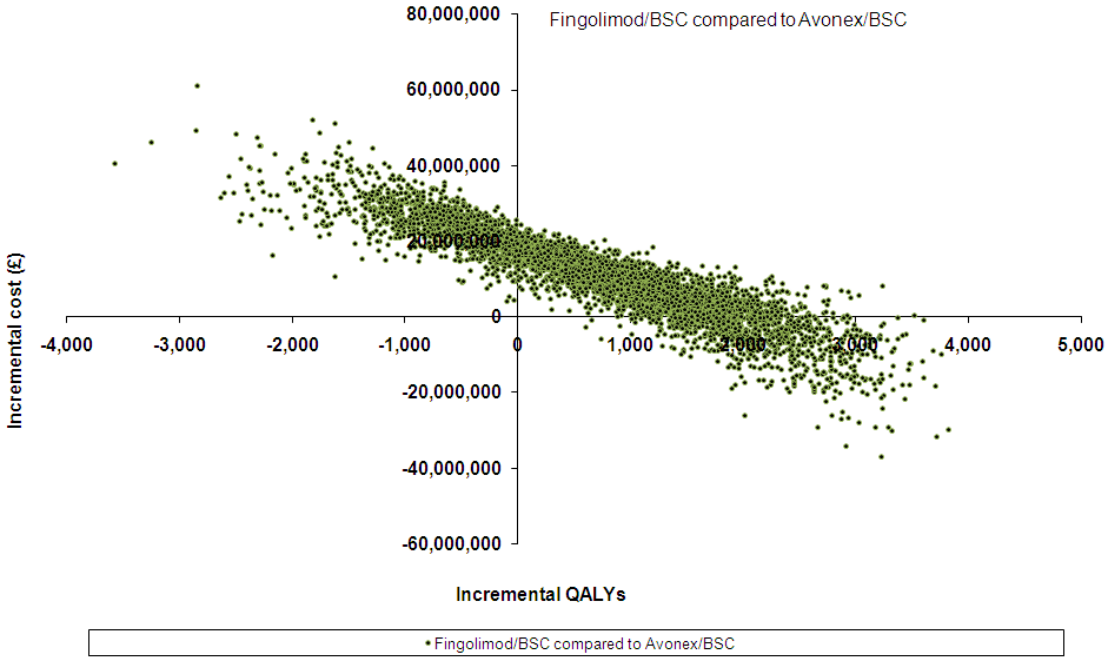
Figure 1: Tornado diagram of base case deterministic analysis (with PAS)



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

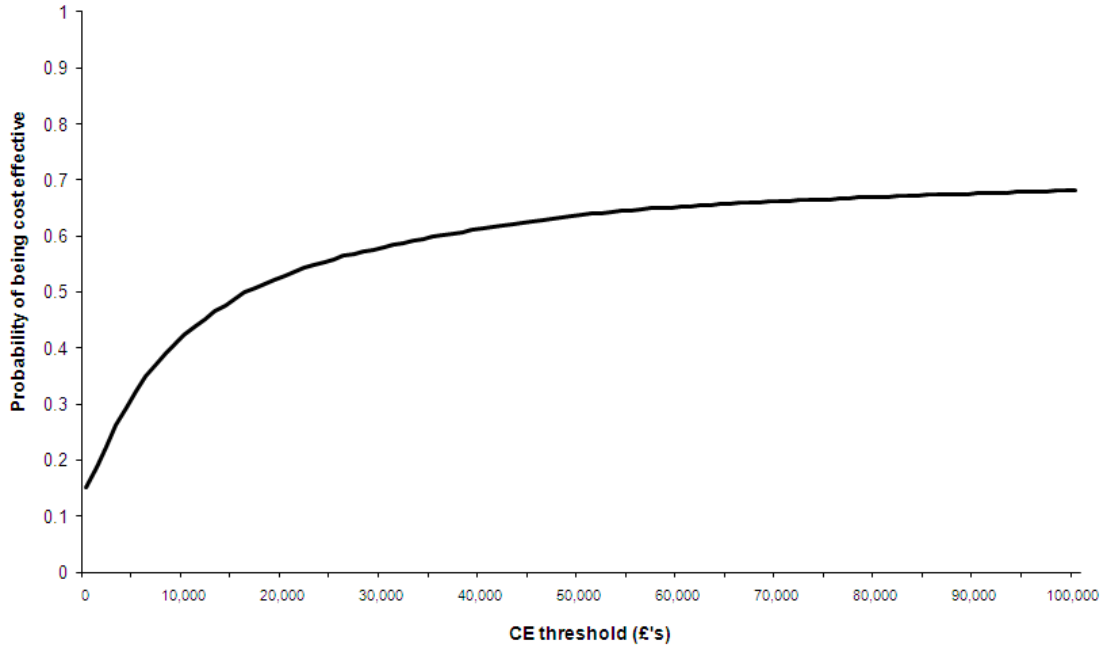
The point estimate of 5000 iterations of the model is an ICER of £15,825 for Gilenya versus Avonex in Population 1b. Figure 2 below shows incremental costs and effect pairs for each of the 5000 iterations of the probabilistic sensitivity analysis (PSA). We can see from the figure that for the vast majority (85%) of iterations of the PSA Gilenya is more effective than Avonex. We can also see that in 26% of iterations Gilenya is both more effective and less costly than Avonex.

Figure 2: PSA Scatter plot (with PAS)



The results of the PSA are also summarised in the cost-effectiveness acceptability curve (CEAC) in Figure 3 below. From the figure we can see that 58% of iterations from the PSA fell below £30,000 per QALY and 52% of iterations fell under £20,000 per QALY.

Figure 3: Cost-Effectiveness Acceptability Curve (with PAS)



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

In the ACD and the ERG report there were discussions about comparisons with other interferon beta products. Novartis has previously highlighted that we can not identify efficacy data for any of the other interferon beta products for Population 1b. This makes any such analysis difficult. However, below we present a series of scenarios to explore the cost effectiveness versus other interferon beta products using assumptions of the efficacy of the interferon beta in patients with a suboptimal response to a previous interferon beta (Population 1b).

Scenario 1 – Comparison with Rebif-44 (Interferon beta-1a)

In the ERG report the ERG undertook an analysis of the cost-effectiveness of Gilenya versus Rebif-44 (Pages 103 to 104). Novartis are cautious about this analysis because it uses efficacy data from EVIDENCE which is a study in first line RRMS patients, and not patients with a suboptimal response to a previous interferon beta (Population 1b). However, we are willing to explore what the impact of the PAS would be on this analysis by the ERG. In the ERG analysis an indirect comparison (Bucher et al., 1997) was applied to the results reported from the EVIDENCE trial in conjunction with results from the FREEDOMS and TRANSFORMS trials to derive relative risks of progression and relapse for Rebif-44 as compared to best supportive care (BSC). Relative Risks for use in the model are shown below, Table 4.

Table 4: Relative Risks reproduced from the ERG report [Table 39 Page 103]

Relative Risk of progression	
Rebif-44 vs. Placebo	0.753
Gilenya vs. Placebo	[redacted]
Relative Risk of Relapse	
Rebif-44 vs. Placebo	0.785
Gilenya vs. Placebo	[redacted]

In the ERG report the withdrawal rate for Rebif-44 is not specified, so Novartis have used the withdrawal rate from the EVIDENCE publication (16/339=0.0467). The withdrawal rate for Gilenya has been taken from the Population 1b subgroup from the placebo controlled trial FREEDOMS and is 2/90=0.022. This gives the following results shown in Table 4.

Table 5: Rebif-44 exploratory analysis (without the PAS)

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Rebif-44	263,055	4.17	—	—	—
Gilenya	326,751	4.94	63,697	0.766	£83,120

When the PAS is applied the cost-per QALY reduces to between the £20k and £30k threshold; the results are shown in Table 6.

Table 6: Rebif-44 exploratory analysis (with the PAS)

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Rebif-44	**263,055**	**4.17**	**—**	**—**	**—**
Gilenya	**284,338**	**4.94**	**21,284**	**0.766**	**27,774**

The main caveat is that the efficacy data for Rebif-44 is for RRMS patients and not those patients with a suboptimal response to a previous interferon beta (Population 1b). This means the efficacy data used in this analysis is likely to over estimate the efficacy of Rebif-44. This means that the cost effectiveness analysis shown in

Table 6 is likely to under estimate the cost effectiveness, i.e. in reality the cost per QALY for Gilenya versus Rebif-44 is likely to be lower than £27,774.

Scenarios 2 and 3 – Comparisons with Beta interferon (Interferon beta-1b) and Rebif-22 (Interferon beta-1a)

In these two analyses we explore the cost effectiveness versus the two remaining interferon beta products: Rebif-22 and Betaferon. As noted above Novartis have been unable to identify efficacy data for the interferons beta other than Avonex in Population 1b. It appears logical that the beta interferons will have a reduced efficacy in patients with a suboptimal response to a previous interferon beta (Population 1b) compared to first line RRMS.

In TRANSFORMS study the primary endpoint annualised relapse rate (ARR) for Avonex in the RRMS population was 0.33. In the subgroup Population 1b, the ARR increased to 0.506. This is an increase of 0.176 or 53% (0.176/0.33).

We could use data from treatment experienced patients as a proxy for patients with a suboptimal response to a previous interferon beta, but the Novartis systematic review did not find any randomised control trial for Rebif-22 which included treatment experienced patients. Out of the eight trials including a Betaferon arm, only 3 did not exclude treatment experienced patients. In none of these trials is the data from the treatment experienced patients separated from the overall population. This means the efficacy of Betaferon in treatment experienced patients is not reported.

In the Novartis submission a Mixed Treatment Comparison (MTC) is described for the RRMS population. For the analysis described below we propose scaling the MTC efficacy to reflect that the

therapy is being considered in patients with a sub-optimal response to a previous beta interferon (Population 1b) and not RRMS.

Selecting the level of scaling is clearly a key assumption. A reduction of 25% in the relative risks from the MTC results in the relative risk rising above 1. This is the point at which the relative risk implies that the therapy is less effective than placebo. It is possible that a therapy could by less effective than placebo, but for the purposes of this analysis Novartis will consider a level of scaling below this.

A reduction of 12.8% scales the Avonex MTC endpoint of relative risk of relapse ([redacted]) to be equal to the relative risk of relapse seen in the indirect comparison presented in the base case ([redacted]). i.e. [redacted] x 1.128 = [redacted]. This indirect data is informed by TRANSFORMS (Gilenya vs. Avonex) and FREEDOMS (Gilenya vs. Placebo) to calculate the efficacy of Avonex vs. Placebo for use in the model. A reduction of 13.7% scales the Avonex MTC endpoint of relative risk of sustained progression ([redacted]) to be equal to the result from the indirect comparison presented in the base case ([redacted]). . i.e. [redacted] x 1.137 = [redacted].

So Novartis have used the midpoint between these two (12.8% and 13.7%) which is 13.25% to adjust the MTC for Rebif-22 and Betaferon. The assumption being that Rebif-22 and Betaferon will experience a reduction in efficacy in Population 1b similar to the reduction observed for Avonex. Systematic reviews have been conducted comparing the beta interferons and have concluded that they have broadly the same efficacy in the treatment of multiple sclerosis.[1,2,3,4] In addition, as part of the NICE MTA of beta interferons and glatiramer acetate the assessment group concluded that the clinical trials do not suggest major differences in the efficacy of different preparations of beta interferon.[5] Table 10 and Table 11 show the adjusted efficacy for Rebif-22 and Betaferon and

are contained in an additional Appendix C at the back of this template.

For Gilenya the efficacy is informed by the FREEDOMS (Gilenya vs. placebo) Population 1b subgroup.

Table 7 is the exploratory results without the PAS and Table 7 is with the PAS applied. The very large caveat is that the efficacy data for Rebif-22 and Betaferon has been scaled from the RRMS population.

In Table 7 and Table 8 at one extreme we have assumed the same efficacy in patients with a suboptimal response to a previous interferon beta (Population 1b) and RRMS; the MTC unscaled columns 3 and 5. The efficacy is very likely to over estimate the efficacy of Rebif-22 and Betaferon. This means that the cost effectiveness analysis shown is likely to under estimate the cost effectiveness, i.e. in reality the cost per QALY for Gilenya versus Rebif-22 and Betaferon is likely to be lower. However, in Table 8 it can be seen that even with this extreme assumption when the PAS is applied the cost-per QALY versus Rebif-22 and Betaferon is only marginally higher than the £30,000 threshold (£34,877 and £37,200 respectively).

If we assume that the MTC result for Rebif-22 and Betaferon would scale by the same degree as Avonex (13.25%) in patients with a suboptimal response to a previous interferon beta (Population 1b) then both the cost-per QALY versus Rebif-22 and Betaferon is below the threshold of £30,000 when the PAS is applied (columns 4 and 6 of Table 8).

Table 7: Exploratory comparison with Betaferon and Rebif-22 (without the PAS)

	Gilenya	Rebif-22	Rebif-22	Betaferon	Betaferon
Efficacy adjustment	N/A	MTC unscaled	MTC -13.25%	MTC unscaled	MTC -13.25%
Total costs (£)	326,745	254,456	258,177	248,670	251,942
Difference in total costs (£)	N/A	72,289	68,569	78,076	74,803
QALYs	4.94	4.08	3.83	3.98	3.77
QALY difference	N/A	0.857	1.109	0.959	1.171
ICER (£)	N/A	84,391	**61,836**	**81,443**	**63,879**

Table 8: Exploratory comparison with Betaferon and Rebif-22 (with the PAS)

	Gilenya	Rebif-22	Rebif-22	Betaferon	Betaferon
Efficacy adjustment	N/A	MTC unscaled	**MTC -13.25%**	MTC unscaled	**MTC -13.25%**
Total costs (£)	284,332	254,456	**258,177**	248,670	251,942
Difference in total costs (£)	N/A	29,876	**26,155**	35,662	32,390
QALYs	4.94	4.08	**3.83**	3.98	3.77
QALY difference	N/A	0.857	**1.109**	0.959	1.171
ICER (£)	N/A	34,877	**23,587**	**37,200**	**27,660**

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable because the scheme is a simple discount

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is

shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 9 demonstrates that when the PAS is applied the ICER for Gilenya versus all of the interferon beta products is below the threshold of £30,000. In Scenario 1 to 3 the efficacy of the comparator is based on assumptions because there is no efficacy data available for suboptimal responders who have been treated on previous beta interferon. In the base-case where efficacy data was available for Avonex the ICER is below the £20,000 threshold.

Therefore, Novartis believes that with the PAS Gilenya is cost-effective in Population 1b versus all of the interferon beta products available.

Table 9: Results showing the impact of PAS on ICERs compared to all the interferon beta products

	Comparator	Source of comparator efficacy data	ICER for intervention versus comparator	
			Without PAS	With PAS
base-case	**Avonex**	**Indirect comparison (Population 1b data)**	**£55,634**	**£10,839**
Scenario 1	Rebif-44	Indirect comparison (RRMS data)	£83,120	£27,774
Scenario 2	Rebif-22	Scaled RRMS MTC data	£61,836	£23,587
Scenario 3	Betaferon	Scaled RRMS MTC data	£63,879	£27,660

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Refer to associated file

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Additional Appendix C: Further details of calculation in the Sensitivity Analysis - Scenario 2

In Section 5.7 of the Novartis submission for Gilenya a mixed-treatment comparison (MTC) is presented. The MTC is for a first line RRMS population. The economic model uses three efficacy inputs relative risk of confirmed disability progression, relative risk of relapse, and treatment discontinuation due to adverse events. Below are the adjustments to the MTC result to account for use in suboptimal responders despite treatment with a previous interferon beta (Population 1b) for the inputs confirmed disability progression, and relapse. For the discontinuations we have not adjusted the MTC result. Intuitively in the sub optimal population you would expect the discontinuation rate to increase compared with RRMS which would reduce the ICER for Gilenya. In the absence of robust evidence that the discontinuations do increase, we have chosen the conservative assumption of not adjusting the discontinuation rates.

Table 10 Relative risk of confirmed disability progression (at 3 months) mixed-treatment comparison results

Relative rate numerator	Relative risk vs. placebo		
	MTC result	Adjusted by 13.25%	Adjusted by 25%
Rebif-22 (Interferon-beta-1a 22 mcg)	[redacted]	[redacted]	[redacted]
Betaferon (Interferon-beta-1b 250 mcg)	[redacted]	[redacted]	[redacted]

Table 11 Relative risk of relapse mixed-treatment comparison results

Relative rate numerator	Relative rate vs. placebo		
	MTC result	Adjusted by 13.25%	Adjusted by 25%
Rebif-22 (Interferon-beta-1a 22 mcg)	[redacted]	[redacted]	[redacted]
Betaferon (Interferon-beta-1b 250 mcg)	[redacted]	[redacted]	[redacted]

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[2] Limmroth et al. 2011. The interferon beta therapies for treatment of relapsing remitting multiple sclerosis: are they equally efficacious? A comparative review of open-label studies evaluating the efficacy, safety, or dosing of different interferon beta formulations alone or in combination. Therapeutic Advances in Neurological Disorders July 25, 2011 1756285611413825

[3] Freedman et al. 2008. Efficacy of Disease-Modifying Therapies in Relapsing Remitting Multiple Sclerosis: A Systematic Comparison. Eur Neurol. 60(1):1-11.

[4] Rice GPA et al. 2009. Cochrane Database Of Systematic reviews (refreshed 2009), issue 4, n CD002002.

[5] NICE MTA 32. Assessment of interferon-beta and glatiramer for the treatment of multiple sclerosis. 2002. Available at: http://www.nice.org.uk/guidance/index.jsp?action=download&o=32265 (Accessed 8/8/2011)