

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Daclizumab for treating relapsing–remitting
multiple sclerosis**

1 Recommendations

1.1 Daclizumab is recommended as an option for treating multiple sclerosis in adults, only if:

- the person has active relapsing–remitting multiple sclerosis previously treated with disease-modifying therapy, or rapidly evolving severe relapsing–remitting multiple sclerosis (that is, at least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI) and
- alemtuzumab is contraindicated or otherwise unsuitable and
- the company provides the drug with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with daclizumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Daclizumab (Zinbryta, Biogen Idec) is a human monoclonal antibody that modulates interleukin-2 signalling to reduce central nervous system pathology, and the occurrence of relapses and disability progression.
Marketing authorisation	Daclizumab is licensed 'in adult patients for the treatment of relapsing forms of multiple sclerosis'.
Adverse reactions	The most commonly reported adverse reactions were rash, increased alanine aminotransferase, depression, nasopharyngitis, upper respiratory tract infection, influenza, oropharyngeal pain and lymphadenopathy. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	A 150 mg subcutaneous injection once monthly.
Price	The list price is £1,596.67 per pre-filled syringe containing 150 mg daclizumab. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of daclizumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Biogen Idec and a review of this submission by the evidence review group. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

- 4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of daclizumab, having considered evidence on the nature of relapsing–remitting multiple sclerosis and the value placed on the benefits of daclizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 The committee heard from the clinical experts and patient experts that relapsing–remitting multiple sclerosis is a chronic, disabling neurological condition. It heard from the patient experts that relapses and residual disability between relapses can substantially reduce quality of life. The committee understood that relapsing–remitting multiple sclerosis can limit people’s ability to work, and to engage in social and family life. The patient experts emphasised that some of the current treatments for the disease had significant drawbacks, including unpleasant side effects (such as injection-site reactions and fatigue). The committee heard that injecting daclizumab once a month at home, compared with injecting more frequently or in hospital, would disrupt routines less and improve emotional wellbeing.

Current treatment pathway, subgroups and comparators

4.3 The committee understood that, currently in the NHS, disease-modifying therapy is used to treat active relapsing–remitting multiple sclerosis. Previous NICE technology appraisal guidance on relapsing–remitting multiple sclerosis has noted that active disease is usually defined as at least 2 clinically significant relapses in the previous 2 years. The committee heard from the clinical experts that, in people with active disease, the first disease-modifying therapy would historically have been a beta interferon or glatiramer acetate, but is now more likely to be a newer treatment such as dimethyl fumarate, teriflunomide or alemtuzumab. The committee heard that the clinical experts considered the various formulations of interferon to be similarly effective. The committee understood that people who have already had disease-modifying therapy and are switching treatment because of an inadequate response are unlikely to have a beta interferon or glatiramer acetate as their second therapy; they would instead have dimethyl fumarate, teriflunomide or alemtuzumab. The clinical experts explained that the choice of treatment varies between patients and between hospitals because there is no single treatment pathway. The committee concluded that it was appropriate to

consider the following subgroups and associated comparators for daclizumab:

- **people with untreated active disease:** beta interferons, glatiramer acetate, dimethyl fumarate, teriflunomide and alemtuzumab
- **people with previously treated active disease:** dimethyl fumarate, teriflunomide and alemtuzumab.

4.4 The committee heard that some people with relapsing–remitting multiple sclerosis have highly active disease. It understood that there is no universally accepted definition of high-activity disease. However, the committee recognised that previous NICE technology appraisal guidance had defined ‘rapidly evolving severe disease’ or ‘highly active disease despite previous treatment’ according to the frequency of relapses, and signs of disease activity on an MRI scan. The clinical experts explained that, in choosing treatment for people with more active disease, clinicians follow NICE guidance, which recommends that patients with rapidly evolving severe multiple sclerosis have treatment with either [natalizumab](#) or [alemtuzumab](#). NICE guidance also recommends that people with highly active disease despite previous treatment are offered alemtuzumab or, if they have previously had treatment with a beta interferon or glatiramer acetate, [fingolimod](#). The committee concluded that it was appropriate to consider the following subgroups and associated comparators for daclizumab:

- **people with rapidly evolving severe disease:** natalizumab and alemtuzumab
- **people with highly active disease despite previous treatment:** fingolimod and alemtuzumab.

4.5 The committee discussed whether the definitions of ‘highly active disease despite previous treatment’ and ‘rapidly evolving severe disease’ presented by the company reflected clinical practice. It noted that these

definitions were based on the clinical trials underpinning the marketing authorisation for daclizumab, which used the following criteria to include patients in either subgroup:

- Highly active disease despite previous treatment:
 - no response after at least 1 year of treatment with a disease-modifying therapy and:
 - ◇ at least 1 relapse in the previous year while on therapy, and at least 9 T2 hyperintense lesions on cranial MRI or
 - ◇ at least 1 gadolinium-enhancing lesion or
 - unchanged or increased relapse rate in the previous year compared with the previous 2 years.
- Rapidly evolving severe multiple sclerosis: at least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI.

The committee noted that these criteria differed from those used in previous NICE technology appraisal guidance for [alemtuzumab](#), [fingolimod](#) and [natalizumab](#). The committee would have preferred the definitions of the subgroups to have been aligned to ensure consistent recommendations. However, it was aware that there was no universally accepted definition of high-activity disease (see section 4.4). Overall, the committee agreed that the clinical and radiological criteria used in the daclizumab clinical trials for both subgroups were broadly similar to those used in previous NICE guidance for relapsing–remitting multiple sclerosis, and captured about the same degree of disease severity. The committee concluded that the definitions used in the daclizumab clinical trials were in line with clinical practice, and that it was appropriate to use them for decision-making in this appraisal.

- 4.6 The committee discussed the factors that may influence patients' choice of treatment. It was aware that the various treatment options available have different methods and schedules of administration. The consultation

comments from patient groups suggested that this may limit the treatment options for some patients. The comments included that alemtuzumab is typically administered as 2 courses of treatment, 12 months apart. The patient experts explained that, once treatment with alemtuzumab is started, its immunosuppressive effects are irreversible. Because of this, some people may not want to take alemtuzumab. In addition, the risk of adverse events with alemtuzumab, including thyroid disorders and thrombocytopaenia, may concern some people enough that they do not want the drug. The committee noted these comments, but also considered that alemtuzumab's dosing schedule and mode of action may appeal to other patients. The committee concluded that individual preferences play a large role in deciding which treatments are appropriate, and it took note of the comments raised about alemtuzumab in its discussion of the evidence.

Clinical effectiveness

Disability progression outcome measure

- 4.7 The committee discussed whether it preferred confirmed disability progression sustained for 3 months or for 6 months as a measure of disease disability. In line with previous appraisals and advice from clinical experts, the committee preferred confirmed disability progression sustained for 6 months. This was because the time taken to recover from a relapse can vary and people may still continue to recover from a relapse after 3 months. However, the committee acknowledged that it was more common for clinical trials to report confirmed disability progression sustained for 3 months. As a result, the company's mixed treatment comparisons using 6-month data excluded some comparators. The committee agreed that, when data for confirmed disability progression sustained for 6 months are available for all comparators in a subgroup, the analyses should use 6-month data. If only 3-month data are available,

then the committee preferred to use this measure rather than exclude available evidence from consideration.

Effectiveness of daclizumab relative to placebo and interferon beta-1a (clinical trial evidence)

4.8 To determine whether daclizumab was effective in the overall population of people (all 4 subgroups combined) with relapsing–remitting multiple sclerosis and active disease, the committee considered the results of the SELECT and DECIDE trials:

- SELECT was a phase II trial that randomly allocated patients to either daclizumab or placebo for up to 1 year (n=621).
- DECIDE was a phase III trial that randomly allocated patients to either daclizumab or interferon beta-1a (Avonex) for 96–144 weeks (n=1,841).

The committee noted that, in the intention-to-treat analyses in both trials, daclizumab reduced the annualised relapse rate (the primary outcome for both trials) and delayed disability progression sustained for 6 months to a clinically important and statistically significant degree (see table 1). The committee concluded that, for the overall population of people with relapsing–remitting multiple sclerosis and active disease, daclizumab was more effective than either placebo or interferon beta-1a (Avonex).

Table 1 Results from SELECT and DECIDE for the overall population

		SELECT versus placebo	DECIDE versus interferon beta-1a (Avonex)
Annualised relapse rate	Rate ratio	0.46	0.55
	95% confidence interval	0.32 to 0.67 p<0.0001	0.47 to 0.65 p<0.001
Confirmed disability progression sustained for 6 months	Hazard ratio	0.24	0.73
	95% confidence interval	0.09 to 0.63 p=0.004	0.55 to 0.98 p=0.03

4.9 The committee noted that, for each of the 4 subgroups listed in sections 4.3 and 4.4, the SELECT and DECIDE trials both showed that daclizumab reduced relapses and delayed the accumulation of disability compared with placebo and interferon beta-1a (Avonex) to a clinically meaningful degree. However, in most subgroups, the effect on disability progression was not statistically significant. The committee concluded that daclizumab was effective at reducing relapses for all subgroups but the effect on disability progression was uncertain.

Effectiveness of daclizumab relative to comparators (mixed treatment comparison)

4.10 The company compared daclizumab with the comparators indirectly for each subgroup using a mixed treatment comparison. In response to consultation, the company revised its mixed treatment comparison by including alemtuzumab as a comparator and using data for daclizumab from the larger DECIDE trial (rather than SELECT). The committee discussed the assumptions that the company made to include alemtuzumab in the evidence network:

- The company assumed that 2 of the beta interferons (Avonex and Rebif-44) were clinically equivalent. The committee agreed that this

was reasonable because the clinical experts considered the various formulations of interferon to be similarly effective (see section 4.3).

- The company assumed that the subgroup populations in the alemtuzumab trials were comparable to those in DECIDE. The committee was aware that the definitions in DECIDE of rapidly evolving severe disease and highly active disease despite previous treatment differed from those used in previous NICE guidance for relapsing–remitting multiple sclerosis (see section 4.5). However, the committee considered that the subgroups were defined based on similar radiological and clinical criteria. It accepted that the subgroup populations were comparable in this appraisal.

The committee concluded that the company’s revised mixed treatment comparison was suitable for decision-making.

- 4.11 The committee discussed the results of the company’s revised mixed treatment comparison. For each subgroup, the company used separate evidence networks to estimate the relative effectiveness of daclizumab on 3 outcomes: annualised relapse rate; disability progression sustained for 3 months; and disability progression sustained for 6 months. Some comparisons between daclizumab and its comparators were not possible because there were no data for a comparator. Among the comparisons presented, daclizumab did not have a statistically significant effect relative to its comparators on any of the outcomes in any of the subgroups. The committee also noted that the confidence intervals were wide, reflecting imprecise and uncertain estimates. It agreed that it would be mindful of this when considering the cost effectiveness of daclizumab.

Cost effectiveness

- 4.12 The committee discussed the company’s economic model and modelling assumptions. It commented that the model was structurally similar to models used in previous NICE technology appraisals, and was appropriate for decision-making. In its response to consultation, the

company submitted an updated model incorporating the committee's preferred assumptions documented at the first appraisal committee meeting.

Treatment stopping rates

4.13 The committee discussed the rate at which patients stop treatment with daclizumab. It understood that in the company's original submission, the company applied the average of the rates in the first 3 years of the DECIDE trial to the first 3 years of the model, and used this average to extrapolate to subsequent years. The evidence review group (ERG) preferred to apply the actual rates from years 1 to 3 to the respective years in the model, and to use the year 3 rate to extrapolate to future years. The committee agreed with the ERG that most adverse events leading to people stopping treatment with daclizumab are likely to occur in the first 2 years of treatment. The committee concluded that it was more appropriate to base the long-term rate of stopping treatment on the rate from the final year of the DECIDE trial. The company reflected this in its updated model.

Waning of treatment efficacy

4.14 The committee discussed whether the effectiveness of daclizumab was likely to remain constant or wane over time. It heard from clinical experts that most treatments for multiple sclerosis become less effective over time, either because of neutralising antibodies or because the disease becomes more severe and resistant to treatment. The committee agreed that the efficacy of daclizumab was unlikely to remain constant over time but the clinical experts advised that the lack of long-term follow-up data for daclizumab meant that it was not known how quickly the efficacy of daclizumab could decline. The committee was aware that, in previous appraisals for multiple sclerosis (such as [alemtuzumab for treating relapsing–remitting multiple sclerosis](#) and [dimethyl fumarate for treating relapsing–remitting multiple sclerosis](#)), the economic modelling included

the treatment effect declining by 25% after 2 years and by 50% after 5 years for all therapies. This waning effect was included in the company's economic model revised in response to consultation. The committee recognised that the modelled therapies have different mechanisms of action, which would affect the rate at which their effect declines over time. However, the committee did not see evidence on the waning effect of individual therapies. Because of this, it accepted the assumptions about the treatment efficacy waning effect used in previous appraisals for all therapies.

Alemtuzumab retreatment

4.15 The committee discussed the company's assumption that patients can have up to 4 courses of alemtuzumab. Although the summary of product characteristics for alemtuzumab states that only 2 courses should be given, the clinical experts explained that some patients are given alemtuzumab in years 3 and 4. The committee concluded that the company appropriately included up to 4 courses of alemtuzumab in its model.

Health-state costs

4.16 The committee discussed the annual costs associated with each expanded disability status scale (EDSS) health state in the model. For the committee's first meeting, the company presented costs from its Burden of Illness study including all investment costs (for example, equipment and home modifications), and community and social care costs (such as home help). For the committee's second meeting, it excluded these costs, to reflect the perspective of the NHS and Personal Social Services (PSS) on costs, as per [NICE's reference case](#). The ERG considered that the NHS and PSS are likely to pay for some investment, community and social care costs. Because of this, it modified the company's costs and included 47% of the investment costs, and 80% of the community and social care costs based on Koebelt et al. (2000). The committee agreed that this

adjustment carried uncertainty. Nevertheless, it concluded that it was appropriate in principle because the ERG's modified costs reflected the perspective of the NHS and PSS more closely than the company's costs excluding all investment, community and social care costs.

4.17 The committee noted that the costs associated with the EDSS health states, particularly the higher health states, differed from those used in previous NICE appraisals for relapsing–remitting multiple sclerosis. Notably, the costs derived from the company's Burden of Illness study, even after the ERG's adjustment, were lower than those used previously. In addition to the Burden of Illness study, previous NICE technology appraisals used other sources of costs for EDSS health state, including:

- the UK MS Survey (using 2011/12 unit costs), which was used in NICE technology appraisal guidance on natalizumab, fingolimod and dimethyl fumarate
- Tyas et al. (2007), which was used in NICE technology appraisal guidance on teriflunomide and alemtuzumab
- Kobelt et al. (2000), which was used in NICE technology appraisal guidance on beta interferon and glatiramer acetate.

In its third meeting, the committee discussed the Burden of Illness study in the context of the historical sources of costs. It considered an addendum to the ERG report, which reviewed and provided cost-effectiveness results using each source.

4.18 The committee noted the following about the different sources of EDSS health-state costs:

- The Burden of Illness study was recently published (2016), and may better reflect changes over time related to costs.
- The costs from the 4 sources were largely consistent up to EDSS health state 6, but varied in the higher health states.

- Kobelt et al. (2000) estimated the highest costs in EDSS health states 7–9 (which were nearly 3 times higher than those from the Burden of Illness study). The committee understood that Kobelt et al. included indirect costs of sickness absence, early retirement and changes in working hours, which would not be borne by the NHS or PSS. Notably, the study did not use recent unit costs, but costs inflated from 1999/2000 prices to 15 years later. Because of these reasons, the committee did not further consider costs from Kobelt et al.
- The UK MS Survey (using 2011/12 unit costs) represented the largest data set (responses from 2,048 people), and estimated NHS and PSS costs, and costs funded by the UK government. The ERG explained that the costs funded by the UK government included costs other than what the NHS and PSS would cover; however, it was unclear what these included. The committee was satisfied that the NHS and PSS costs estimated from the UK MS Survey could be used in this appraisal.
- Tyas et al. (2007) reflected another analysis of data from the UK MS Survey. However, it reported only costs funded by the UK government. Because of this, the committee did not consider Tyas et al. further.

Of the above sources, the committee agreed that the company's Burden of Illness study, as adjusted by the ERG, was appropriate to use as a starting point for making recommendations. However, it acknowledged the uncertainty associated with the ERG's adjustment of the investment costs, and community and social care costs to reflect the perspective of the NHS and PSS. The committee also agreed that it would compare the analyses based on the Burden of Illness study with those based on the UK MS Survey, giving extra consideration where differences exist, to ensure a reasonable degree of consistency in decision-making across technology appraisals.

Natural history of the disease in subgroup analyses

4.19 The committee noted that the company initially used registry data from British Columbia and the placebo group from SELECT to model the natural history of relapsing–remitting multiple sclerosis for all subgroups. This meant the speed of accumulating disability and moving to higher EDSS states was the same across all subgroups. The clinical experts did not find this assumption plausible because people with high disease activity or rapidly evolving disease usually progress to higher EDSS states faster than people with less active disease. In response to consultation, the company continued to use the British Columbia dataset to model the natural history of disease for the less active subgroups, but submitted alternative sources of data for the highly active subgroups:

- For highly active disease despite previous treatment: the placebo arms of the DEFINE and CONFIRM trials.
- For rapidly evolving severe disease: the placebo arm of the rapidly evolving severe subgroup of the AFFIRM trial.

The committee concluded that these approaches appropriately captured the faster rate of disease progression in the highly active subgroups.

4.20 The committee noted the company's assumption that EDSS scores worsen by 1.0 point when people moved from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis in the model. The ERG preferred not to make this assumption for the less active subgroups in its modified base case. This was because the British Columbia dataset, which was used to model the natural history of relapsing–remitting disease for these subgroups, included people with secondary progressive disease. Therefore, the drop in EDSS score as the disease progresses to secondary progressive multiple sclerosis would already have been captured, at least partly, within the British Columbia dataset, and applying the drop would exaggerate disability progression. The committee agreed that the ERG had appropriately removed the assumption that the health

state worsened by 1.0 point when moving to secondary progressive disease in its modified base case.

Caregiver quality of life

4.21 The committee noted that the company, in response to consultation, removed the quality-of-life decrement reflecting the burden that carers of people with multiple sclerosis experience. In its modified base case, the ERG continued to apply a decrease in the caregiver utility. The decrement varied by EDSS health state, with a maximum decrement of -0.05 quality-adjusted life years (QALYs) corresponding to caring for someone in the highest EDSS health state. The committee was aware that previous NICE guidance for relapsing–remitting multiple sclerosis included disutility for caregivers. The committee agreed that it was important to recognise the impact that caring for people with multiple sclerosis has on caregivers.

Innovation

4.22 The committee heard from the patient experts that daclizumab is given once monthly by subcutaneous injection and this offered advantages over alternative treatments that need to be given more frequently or by intramuscular injection. Patients expected that daclizumab would cause fewer injection-site related side effects, and less disruption to daily routines. The committee agreed that these benefits would be welcomed by patients, but noted that other treatments for multiple sclerosis also offer these benefits, for example, those taken orally or alemtuzumab, which is given intravenously up to only 4 times in a lifetime. The committee noted that the company considered daclizumab's mechanism of action to be unique in the treatment of relapsing–remitting multiple sclerosis. However, the clinical experts did not consider daclizumab to represent a step change in multiple sclerosis treatment because its effectiveness and safety profile were similar to other treatments currently available in the NHS. The committee concluded that it had not been presented with any

evidence of additional benefits of daclizumab that were not captured in the QALYs.

Cost-effectiveness results

- 4.23 The committee considered results for each of the 4 subgroups (see sections 4.3 and 4.4). Daclizumab and some of the comparator drugs are offered by their respective companies to the NHS with discounts. Because the comparator discounts are confidential (and not known by Biogen Idec), the ERG recalculated the company's analyses using the discounts for interferon beta-1a (Avonex and Rebif), glatiramer acetate, dimethyl fumarate, fingolimod and teriflunomide. The results are therefore confidential and cannot be reported here.
- 4.24 The committee was presented with the company's base case, and the ERG's modified base case, both including the confidential comparator discounts. Overall, the committee agreed that it was more appropriate to use the ERG's modified base case for decision-making. This was because the ERG's modified base case reflected the committee's preferred assumptions. In particular, the ERG:
- used revised health-state costs incorporating some investment, and community and social care costs (see section 4.16)
 - did not assume that transitioning to secondary progressive disease was associated with a 1.0 point worsening in EDSS (see section 4.20)
 - incorporated a caregiver quality-of-life decrement (see section 4.21).
- 4.25 When the evidence allowed, the company and the ERG presented cost-effectiveness results based on confirmed disability progression sustained for 3 months and, separately, based on confirmed disability progression sustained for 6 months. In line with its previous conclusion, the committee agreed that the analyses should use 6-month data when these were available, and only use 3-month data if there were no 6-month data (see section 4.7). When there were data to estimate costs and QALYs for all

relevant comparators in a given analysis, the committee was presented with both pairwise, and fully incremental cost-effectiveness ratios (ICERs). When there were no data to estimate the relative effectiveness of one of the comparators, and hence the QALYs associated with it, the committee was only presented with pairwise ICERs comparing daclizumab with each of the remaining comparators individually. The cost-effectiveness results available to the committee are summarised in table 2.

Table 2 Cost-effectiveness results available for each subgroup

Subgroup	3-month disability progression data		6-month disability progression data	
	Incremental ICERs	Pairwise ICERs	Incremental ICERs	Pairwise ICERs
-				
Untreated active disease	✓	✓	x ¹	✓ ²
Previously treated active disease	x	x	x ¹	✓ ²
Highly active disease despite prior treatment	✓	✓	x	x
Rapidly evolving severe disease	x	x	✓	✓
¹ No data to estimate the 6-month disability progression hazard ratio for teriflunomide. ² Except for the comparison with teriflunomide. Abbreviation: ICER, incremental cost-effectiveness ratio				

The committee was aware that all of the analyses presented by the ERG were deterministic. As such, they did not take into account parameter uncertainty, such as that surrounding the hazard ratios estimated in the mixed treatment comparison (see section 4.11).

4.26 The committee noted that, across all subgroups, daclizumab was not cost effective compared with alemtuzumab using costs from the company's Burden of Illness study adjusted by the ERG:

- **Untreated active disease:** daclizumab was dominated by alemtuzumab (that is, was less effective and more expensive than alemtuzumab).

- **Previously treated active disease:** daclizumab was less expensive and less effective than alemtuzumab; it had an ICER of £789 saved per QALY lost. The committee agreed that the savings associated with daclizumab were insufficient to justify the QALY loss.
- **Highly active disease despite previous treatment:** alemtuzumab was more cost effective than daclizumab at a maximum acceptable ICER of £20,000–£30,000 per QALY gained, with an incremental ICER of £18,004 per QALY gained.
- **Rapidly evolving severe disease:** daclizumab was dominated by alemtuzumab.

The committee noted that using costs from the UK MS Survey would not change any of the above conclusions because either daclizumab would be dominated by alemtuzumab (in people with untreated active disease, previously treated active disease and rapidly evolving severe disease) or alemtuzumab would remain more cost effective than daclizumab with an incremental ICER of £9,638 per QALY gained (in people with highly active disease despite previous treatment). The committee concluded that daclizumab did not represent a cost-effective use of NHS resources when alemtuzumab was a treatment option.

People in whom alemtuzumab is contraindicated or otherwise unsuitable

4.27 The committee was aware that alemtuzumab is contraindicated in some patient groups (for example, people who have HIV). The committee also recalled the comments from consultation suggesting that some people have concerns about taking alemtuzumab (see section 4.6). Because of this, the committee agreed to consider whether daclizumab was cost effective compared with the remaining treatment options for people in whom alemtuzumab is contraindicated or otherwise unsuitable. For each subgroup, the committee noted the following pairwise comparisons for daclizumab from the ERG's modified base case:

- **Untreated active disease:** the remaining treatment options for this group include beta interferons, glatiramer acetate, dimethyl fumarate and teriflunomide. Compared with all of these alternatives, the pairwise ICER for daclizumab exceeded £30,000 per QALY gained when using costs from the Burden of Illness study. This was also the case when using costs from the UK MS Survey, except for the comparison of daclizumab with teriflunomide. The committee noted that people with untreated active disease have more treatment options than other groups of people. Also, daclizumab was not cost effective compared with any of the comparators using costs from the Burden of Illness study, and most of the comparators using costs from the UK MS Survey. Therefore, the committee concluded that daclizumab does not represent a cost-effective use of NHS resources for people with untreated active disease in whom alemtuzumab is contraindicated or otherwise unsuitable.
- **Previously treated active disease:** the remaining treatment options for this group include dimethyl fumarate and teriflunomide. Daclizumab could not be compared with teriflunomide because there were no data to estimate the 6-month disability progression hazard ratio for teriflunomide. The ICER for daclizumab compared with dimethyl fumarate was between £20,000–30,000 per QALY gained using costs from the Burden of Illness study, and was lower using costs from the UK MS Survey. The committee concluded that daclizumab is a cost-effective use of NHS resources for people with previously treated active disease in whom alemtuzumab is contraindicated or otherwise unsuitable.
- **Highly active disease despite previous treatment:** the only alternative treatment option for this group is fingolimod. The committee noted that daclizumab was less costly but also less effective than fingolimod. Although the pairwise ICER for daclizumab was less than £20,000 saved per QALY lost, the QALY difference between the 2 alternatives was very small, and so the risk to the NHS associated

with the decision was small. The ICER was lower (indicating it was less cost effective) using costs from the UK MS Survey. The committee was aware that people with highly active disease despite previous treatment in whom alemtuzumab is contraindicated or otherwise unsuitable represent a small group with severe disease, and high burden of illness on both the patient and the carer. Together with the limited options available, this meant that there was high unmet need in this group, and daclizumab would be valued by patients and clinicians. The committee therefore concluded that daclizumab is a cost-effective use of NHS resources for people with highly active disease despite previous treatment in whom alemtuzumab is contraindicated or otherwise unsuitable.

- **Rapidly evolving severe disease:** the only alternative treatment option for this group is natalizumab. Daclizumab was more effective and less expensive than natalizumab using any source of costs. The committee therefore concluded that daclizumab is a cost-effective use of NHS resources for people with rapidly evolving severe disease in whom alemtuzumab is contraindicated or otherwise unsuitable.

Committee conclusions

4.28 On the basis of the discussion in sections 4.26 and 4.27, the committee concluded that daclizumab represents a cost-effective use of NHS resources for treating relapsing–remitting multiple sclerosis in adults, only if:

- the person has active disease previously treated with disease-modifying therapy, or rapidly evolving severe disease and
- treatment with alemtuzumab is contraindicated or otherwise unsuitable.

The committee recalled that the definitions of the subgroups were based on the clinical trials underpinning the marketing authorisation for daclizumab. It concluded that these definitions were in line with clinical

practice, and appropriate to use for decision-making in this appraisal (see section 4.5).

Pharmaceutical Price Regulation Scheme 2014

4.29 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014 and, in particular, the PPRS payment mechanism. It accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The committee heard nothing to suggest that it should take a different view for this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title: Daclizumab for treating relapsing–remitting multiple sclerosis	Section
Key conclusion		
Daclizumab is recommended as an option for treating multiple sclerosis in adults, only if: <ul style="list-style-type: none"> • the person has active relapsing–remitting multiple sclerosis previously treated with disease-modifying therapy, or rapidly evolving severe relapsing–remitting multiple sclerosis (that is, at least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI) and • alemtuzumab is contraindicated or otherwise unsuitable and • the company provides the drug with the discount agreed in the patient access scheme. 		1.1

<p>The committee agreed that it would compare the analyses based on the Burden of Illness study with those based on the UK MS Survey, giving extra consideration where differences exist, to ensure a reasonable degree of consistency in decision-making across technology appraisals.</p>		4.17, 4.18
<p>The committee concluded that daclizumab did not represent a cost-effective use of NHS resources when alemtuzumab was a treatment option.</p>		4.26
<p>The committee concluded that daclizumab represented a cost-effective use of NHS resources for active disease previously treated with disease-modifying therapy, and rapidly evolving severe disease, when alemtuzumab was not a treatment option.</p>		4.27
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>People with multiple sclerosis that is suitable for disease-modifying therapy have historically been offered a beta interferon or glatiramer acetate, but are now usually offered an oral drug (such as dimethyl fumarate or teriflunomide) or alemtuzumab. People switching to a different therapy for efficacy reasons are usually offered dimethyl fumarate, teriflunomide or alemtuzumab.</p>	4.3
	<p>People with highly active disease, despite treatment with a disease-modifying therapy, are offered alemtuzumab or fingolimod. People with rapidly evolving severe disease are offered alemtuzumab or natalizumab.</p>	4.4

The technology		
Proposed benefits of the technology	Daclizumab statistically significantly reduces the annualised relapse rate and confirmed disability progression compared with placebo and interferon beta-1a.	4.9
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	<p>Patient experts advised that daclizumab's monthly subcutaneous injection regimen reduced unpleasant injection-related side effects and caused less disruption to daily routines.</p> <p>Clinical experts did not consider daclizumab to represent a step change in multiple sclerosis treatment.</p>	4.22
What is the position of the treatment in the pathway of care for the condition?	Daclizumab could be used as initial or subsequent therapy in any of the subgroups identified in the scope.	4.3, 4.4
Adverse reactions	The most commonly reported adverse reactions were rash, increased alanine aminotransferase, depression, nasopharyngitis, upper respiratory tract infection, influenza, oropharyngeal pain and lymphadenopathy.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The evidence came from 2 randomised controlled trials: SELECT, a phase II dose-ranging study that compared daclizumab with	4.8

	<p>placebo (n=621); and DECIDE, a phase III study in which patients had treatment with daclizumab or interferon beta-1a (n=1,841).</p>	
<p>Relevance to general clinical practice in the NHS</p>	<p>There were some differences between the definitions of the ‘highly active despite previous treatment’ and ‘rapidly evolving severe’ groups in the daclizumab clinical trials and the definitions used in previous NICE guidance for relapsing–remitting multiple sclerosis. The committee concluded that the definitions used in daclizumab’s clinical trials were in line with clinical practice.</p>	<p>4.5</p>

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>For each of the 4 subgroups, the SELECT and DECIDE trials both showed that daclizumab reduced relapses and delayed the accumulation of disability compared with placebo and interferon beta-1a (Avonex) to a clinically meaningful degree. However, in most subgroups, the treatment effect was not statistically significant. The results of the subgroup analyses based on the mixed treatment comparisons also showed no statistically significant difference between daclizumab and its comparators.</p>	<p>4.9, 4.11</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>For the overall population, daclizumab statistically significantly reduced the rate of relapses and confirmed disability progression sustained for 6 months compared with placebo and interferon beta-1a (Avonex).</p> <p>For each of the 4 subgroups, the SELECT and DECIDE trials both showed that daclizumab reduced relapses and delayed the accumulation of disability compared with placebo and interferon beta-1a (Avonex). However, in most subgroups, the treatment effect was not statistically significant, and the results of the subgroup analyses based on the mixed treatment comparisons also showed no statistically significant difference between daclizumab and its comparators.</p>	<p>4.8, 4.9</p>
<p>Evidence for cost effectiveness</p>		

Availability and nature of evidence	The company submitted an economic model that was structurally similar to other models used in previous NICE technology appraisals.	4.12
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<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The company's revised economic model included a treatment efficacy waning effect, which was applied to all comparators. The committee recognised that these therapies have different mechanisms of action, which would affect the rate at which their effect declines over time. However, the committee did not see evidence on the waning effect of the individual therapies and accepted the assumption to apply the same effect across all comparators.</p>	<p>4.14</p>
	<p>The company excluded all investment costs, and community and social care costs to reflect the perspective of the NHS and Personal Social Services (PSS) on costs. The evidence review group (ERG) considered that the NHS and PSS are likely to pay for some of these costs, and modified the company's estimates to reflect this. The committee concluded that the ERG's modified costs reflected the perspective of the NHS and PSS more closely than the company's costs, although it agreed that the ERG's adjustment of costs carried uncertainty.</p>	<p>4.16</p>
	<p>The committee noted that the costs associated with the EDSS health states differed from those used in previous NICE appraisals for relapsing–remitting multiple sclerosis. Because of this, it discussed the</p>	<p>4.17</p>

	Burden of Illness study in the context of the historical sources of costs.	
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Patient experts advised that daclizumab’s monthly subcutaneous injection regimen reduces unpleasant injection-related side effects and causes less disruption to daily routines. The committee noted that other treatments for multiple sclerosis also offer these benefits.</p> <p>The committee concluded that it had not been presented with any evidence of additional benefits of daclizumab that were not captured in the quality-adjusted life year.</p>	4.22
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee concluded that daclizumab is cost effective for people in whom alemtuzumab is contraindicated or otherwise unsuitable, if they have active relapsing–remitting multiple sclerosis previously treated with disease-modifying therapy, or rapidly evolving severe relapsing–remitting multiple sclerosis.</p>	4.27
<p>What are the key drivers of cost effectiveness?</p>	<ul style="list-style-type: none"> • Hazard ratios for disability progression • Health-state costs 	<p>4.8</p> <p>4.16–</p> <p>4.18</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>When alemtuzumab is an option (using costs from the Burden of Illness study):</p> <ul style="list-style-type: none"> • Untreated active disease: alemtuzumab dominated daclizumab (that is was more effective and less expensive than daclizumab). • Previously treated active disease: £789 saved per QALY lost for daclizumab compared with alemtuzumab. • Highly active disease despite previous treatment: £18,004 per QALY gained for alemtuzumab compared with daclizumab (alemtuzumab was more cost effective than daclizumab in the incremental analysis). • Rapidly evolving severe disease: alemtuzumab dominated daclizumab. 	<p>4.26</p>
	<p>When alemtuzumab is contraindicated or otherwise unsuitable (using costs from the Burden of Illness study):</p> <ul style="list-style-type: none"> • Untreated active disease: above £30,000 per QALY gained for daclizumab compared with beta interferons, glatiramer acetate, dimethyl fumarate and teriflunomide. • Previously treated active disease: between £20,000–30,000 per QALY gained for daclizumab compared with dimethyl fumarate. • Highly active disease despite previous treatment: less than £20,000 saved per 	<p>4.27</p>

	<p>QALY lost for daclizumab compared with fingolimod.</p> <ul style="list-style-type: none"> • Rapidly evolving severe disease: daclizumab dominated natalizumab. 	
Additional factors taken into account		
Patient access schemes (PPRS)	There are patient access schemes for daclizumab and several of the comparators, as well as commercial access arrangements for some of the beta interferons and glatiramer acetate. The ERG recalculated the company's analyses using these discounts.	4.23
End-of-life considerations	Not applicable	-
Equalities considerations and social value judgements	During scoping, a clinician pointed out that people of African Caribbean and Asian family background who have multiple sclerosis tend to have more severe and quicker progressing disease. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. The committee did discuss subgroups of people who have rapidly evolving or highly active disease.	-

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning

groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that daclizumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and Biogen Idec have agreed that daclizumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to **[NICE to add details at time of publication]**

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
November 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ross Dent

Technical Lead

Rosie Lovett/Ahmed Elsada

Technical Adviser

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Project Manager

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