NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Daclizumab for treating relapsing–remitting multiple sclerosis

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daclizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using daclizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 21 October 2016

Second appraisal committee meeting: 2 November 2016

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Daclizumab is not recommended within its marketing authorisation for treating relapsing forms of multiple sclerosis in adults.

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. If daclizumab had been recommended, this scheme would provide 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 would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) 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 there were significant drawbacks associated with some of the current treatments for the disease, 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 considered suitable treatment for 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 oral medication such as dimethyl fumarate or teriflunomide. 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 more active disease, meaning they have more frequent relapses or show more signs of disease activity on an MRI scan. They can have rapidly-evolving severe disease or highly active disease despite previous treatment (see table 1 for definitions).

Table 1 Types of more active multiple sclerosis

Type of more active disease	Definition
Rapidly-evolving severe multiple sclerosis	At least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI.
Highly active disease despite previous treatment	Failure to respond to at least 1 year of treatment with a disease-modifying therapy, 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.

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 In addition to results for the 4 subgroups defined above, the company also submitted results for all people with more active disease. That is, the company combined the 2 subgroups of people with rapidly-evolving severe disease and highly active disease despite previous treatment. The committee understood that it made sense from a clinical perspective to combine these 2 subgroups because clinical experts view these patients as similar. However, the committee did not find this approach helpful for decision-making because treatment options differ for people with rapidly-evolving or highly active disease (see section 4.4). The committee also understood that clinicians would be unlikely to offer patients the company's chosen comparator, interferon beta-1a (Avonex). For these reasons, the committee preferred to consider the 2 subgroups of patients with more active separately and did not consider further the expanded subgroup of all people with more active disease.

Stopping treatment

4.6 The committee discussed at what point people stop disease-modifying therapy. It heard from clinical experts that most people stop treatment when their accumulated disability prevents them from walking. This corresponds to an expanded disability status scale (EDSS) score of 7.0 and above. The clinical experts explained that there is no consensus about whether to continue treatment after people develop secondary progressive multiple sclerosis. The committee understood that the difference between relapsing–remitting and secondary progressive

multiple sclerosis is that, in the former, disability accumulates because of incomplete recovery from relapses and, in the latter, there is sustained build-up of disability independent of any relapses. Some people stop treatment when they develop secondary progressive disease whereas others may continue treatment, especially if they continue to have relapses. The committee noted that the company did not present evidence on the effectiveness of continuing daclizumab treatment for people with secondary progressive multiple sclerosis, and the model assumed that patients stop treatment when they develop secondary progressive disease. Accordingly, the committee did not consider further daclizumab for people with secondary progressive multiple sclerosis.

Clinical effectiveness

4.7 The committee considered evidence from 2 randomised controlled 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).

Eligibility criteria and number of relapses

4.8 The committee noted that SELECT and DECIDE recruited people who had had at least 1 relapse in the previous year. The committee understood that daclizumab was licensed for treating multiple sclerosis in people who met this criterion. In contrast, previous NICE guidance (such as dimethyl fumarate for treating relapsing–remitting multiple sclerosis and teriflunomide for treating relapsing–remitting multiple sclerosis) recommended that treatment with disease-modifying therapy should be offered only to people who had had 2 relapses in the previous 2 years. The committee was unsure whether the company was proposing that daclizumab should be offered to people who have had at least 1 relapse in the previous year (meaning that people would start treatment with a disease-modifying therapy earlier in the course of their disease than has

previously been the case). The committee invited the company to clarify this aspect of its submission.

Disability progression outcome measure

4.9 The committee discussed which measure of disability progression it preferred: confirmed disability progression sustained for 3 months or for 6 months. In line with previous appraisals and advice from clinical experts, the committee preferred to use 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 some comparators from consideration.

Trial results and mixed treatment comparisons

4.10 To determine whether daclizumab was effective in the overall population of people with relapsing–remitting multiple sclerosis and active disease, the committee considered the results of the DECIDE and SELECT trials. The committee noted that, in the intention-to-treat analyses for the overall population in both trials, daclizumab statistically significantly reduced the annualised relapse rate (the primary outcome for both trials) and delayed disability progression sustained for 6 months.

		SELECT vs. placebo	DECIDE vs. 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

The committee concluded that, for the overall population of people with relapsing–remitting multiple sclerosis and active disease, daclizumab was clinically effective compared with placebo and interferon beta-1a (Avonex). However, the committee recognised that it needed to see the results of a mixed treatment comparison comparing daclizumab with all of the relevant comparators in each subgroup to make a decision about whether daclizumab was clinically effective.

4.11 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). However, in most subgroups, the treatment effect was not statistically significant. The company used a mixed treatment comparison to compare the clinical effectiveness of daclizumab and the comparators for each subgroup. The mixed treatment comparison mainly used data from the SELECT trial to provide an estimate of the clinical effectiveness of daclizumab. The committee was concerned that the subgroup analyses of the SELECT trial were informed by small numbers of patients. For example, SELECT enrolled only 34 patients with rapidly-evolving severe multiple sclerosis and only 32 patients with highly active disease despite treatment; the sample sizes for these subgroups in DECIDE were substantially larger (184 patients and 272 patients respectively). The committee concluded

that there was substantial uncertainty about the effectiveness of daclizumab for the subgroups listed in the scope, and that the most robust data for all subgroups came from DECIDE.

4.12 The committee noted that alemtuzumab was included in the NICE scope as a comparator for each of the 4 subgroups. The committee acknowledged that, for the overall population, the company provided a comparison of daclizumab with alemtuzumab. However, the company did not incorporate alemtuzumab into the mixed treatment comparisons for the subgroups because it could not connect the relevant trial data for alemtuzumab to the subgroup evidence networks. The committee was aware that the mixed treatment comparison for the overall population showed that alemtuzumab was the most effective treatment. The committee heard from the clinical experts that alemtuzumab is used in clinical practice and that it was important to include alemtuzumab as a comparator in the appraisal of daclizumab. The committee concluded that the company's mixed treatment comparisons for subgroups were not fully informative because they excluded alemtuzumab.

4.13 To provide evidence relevant to the NHS, the committee invited the company to submit a new mixed treatment comparison for each of the subgroups that:

- used the DECIDE clinical trial results for daclizumab
- included alemtuzumab as a comparator.

The committee considered that possible approaches might include:

- pooling the data for all beta interferons
- treating the beta interferons as a single class of drugs (that is, assuming their treatment effects are similar but not identical)
- inferring hazard ratios for alemtuzumab in subgroups based on the correlation between intention-to-treat results and subgroup results in other trials.

Treatment efficacy waning effect

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 the person's immune system develops neutralising antibodies or because the disease becomes more severe and resistant to treatment. The committee concluded that the efficacy of daclizumab was unlikely to remain constant over time, as assumed in the company's economic model. 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 would decline. Given the lack of evidence, the committee agreed that it was appropriate to assume a reduction in treatment effect of 25% after 2 years and of 50% after 5 years because this was consistent with previous appraisals (such as alemtuzumab for treating relapsing–remitting multiple sclerosis and dimethyl fumarate for treating relapsing-remitting multiple sclerosis). The committee noted that a scenario analysis from the evidence review group (ERG) had included this waning effect.

Cost effectiveness

4.15 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.

Treatment stopping rates

4.16 The committee discussed the rate at which patients stop treatment with daclizumab. It understood that the company applied the average of the rates in first 3 years of the DECIDE trial to the first 3 years of the model, and used the average to extrapolate to subsequent years. The 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 heard from the company that it thought the ERG's approach was not appropriate because few patients had a full 3 years of follow-up, meaning that the 3-year data were 'skewed'. The committee did not agree that variable follow-up times meant that the data were biased. It 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.

Mortality

4.17 The committee discussed in detail the multipliers used to account for the greater risk of death in people with multiple sclerosis compared with the general population. It acknowledged that there was uncertainty about mortality rates because both the company and ERG used historic data sets that likely differed from current populations. The committee was concerned that both the company and ERG may have overestimated mortality risk associated with lower EDSS health states, in which the clinical experts advised that mortality was not substantially greater than the general population. However, the committee agreed that, because the difference in life years gained between treatments was small, mortality was not a key driver of the model.

Drug costs

4.18 The company assumed in its model that daclizumab is given monthly (that is, 12 doses are given per year). The committee noted that the ERG preferred to assume that daclizumab is given every 4 weeks (that is, 13 doses are given per year) to reflect the clinical trials. The clinical experts confirmed that, in the NHS, daclizumab would be given monthly, in line with the summary of product characteristics. The committee accepted that the modelling should assume 12 doses of daclizumab are given per year, as the company did in its base case.

Alemtuzumab administration

4.19 The committee discussed the company's assumption that patients can have up to 4 doses of alemtuzumab. The ERG was concerned that the summary of product characteristics for alemtuzumab states that only 2 doses should be given. The ERG was also concerned that the company had inappropriately applied a half-cycle correction to the costs of alemtuzumab because it is given at the start of a year. 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 doses of alemtuzumab in its model. However, the committee agreed that the company should not apply a half-cycle correction to the costs of alemtuzumab in the model (to be consistent with alemtuzumab for treating relapsing–remitting multiple sclerosis).

4.20 The committee heard that the company assumed that 15 days and 9 days of treatment with corticosteroids are needed before the first 5-day course and the second 3-day course of alemtuzumab respectively. The company also assumed that, in any year when alemtuzumab is given, patients would take antihistamines daily for the whole year. The clinical experts advised that each course of alemtuzumab would only need 3 days of pre-treatment with both corticosteroids and antihistamines. The clinical advice was in line with the summary of product characteristics and the committee agreed that this should be reflected in the model, although it had not been presented with this analysis.

Health-state costs

4.21 The committee discussed the annual costs associated with each EDSS health state in the model. The company used costs from its Burden of illness study, but advised the committee during the meeting that it had included some non-NHS costs and personal social services costs in error. The costs included by mistake included informal care provided by friends and family, and some aids and adaptations for people's homes, which are

likely to be paid for by patients. However, the committee noted that the costs in the ERG's base case, based on the company's adjusted Karampampa et al. (2012) costs, were substantially lower than the costs that had been used in previous appraisals. This was particularly true for higher EDSS health states (compared with, for example, alemtuzumab for treating relapsing–remitting multiple sclerosis, dimethyl fumarate for treating relapsing–remitting multiple sclerosis). The committee invited the company to submit a model with revised costs from the Burden of illness study, adjusted to remove non-NHS and personal social services costs. The committee also requested that the company compare its cost estimates (from both the Burden of illness and Karampampa et al. studies) with the costs used in previous NICE appraisals and explain any substantial differences.

Natural history of the disease in subgroup analyses

4.22 The committee noted that, for all analyses, the company used the same longitudinal data to model the natural history of multiple sclerosis without treatment. Specifically, the company used registry data from British Columbia and the placebo group from SELECT. The committee was concerned that this meant the speed of accumulating disability and moving to higher EDSS states was the same across all subgroup analyses. The clinical experts explained that this assumption was not plausible because people with high disease activity or rapidly-evolving disease usually progress to higher EDSS states at a faster rate than people with less active disease. The committee understood that it was difficult to alter the model because: the long-term observational datasets did not distinguish between people with moderate and high disease activity; and more recent datasets such as the DECIDE trial had relatively short follow-up times. However, the committee concluded that it would prefer to see analyses in which the subgroups with more active disease progressed to higher EDSS states at a quicker rate than the subgroups with less active disease.

Cost-effectiveness results

4.23 The committee discussed the cost-effectiveness results for daclizumab. It agreed that the modelling was subject to a very high degree of uncertainty. This was because SELECT was used for the subgroup mixed treatment comparisons and because of the lack of comparisons with alemtuzumab for any of the subgroups.

4.24 The company presented cost-effectiveness results for the whole population of people with relapsing–remitting multiple sclerosis (including people with active, rapidly-evolving severe and highly active disease). The committee noted that this population was outside the NICE scope and did not reflect what it had heard from the clinical experts about treatments differing between different subgroups of people with relapsing–remitting multiple sclerosis. However, the committee agreed that this population represented the intention-to-treat population of the SELECT trial and included alemtuzumab as a comparator. Although the committee discussed these results, it preferred to use the subgroup analyses for decision making because the patients in subgroups had different levels of disease activity and the relevant comparators were different for each subgroup.

4.25 The committee considered results for each of 4 subgroups (see sections 4.3 and 4.4). Daclizumab and some of the comparators 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 exact results are confidential and cannot be reported here.

4.26 The committee discussed the cost effectiveness of daclizumab in the 2 subgroups of patients without more active disease who: 1. had not previously had treatment, and 2. had previously had treatment. The

committee noted that some of the company's pairwise deterministic incremental cost-effectiveness ratios (ICERs) were lower than £30,000 per quality-adjusted life year (QALY) gained (the exact results depended on the comparator). However, none of the ERG's pairwise ICERs were lower than £30,000 per QALY gained and, in both the company's and ERG's fully incremental analysis, the ICERs for daclizumab were very high. Furthermore, the committee was not presented with a comparison of daclizumab with alemtuzumab. The committee concluded that daclizumab was not a cost-effective use of NHS resources for patients without more active disease who had or had not previously had treatment.

4.27 The committee was concerned that the model was informed by very small numbers of patients having daclizumab from the SELECT trial in the subgroups with highly active disease despite previous treatment (n=32) and rapidly-evolving severe disease (n=34). The committee was also concerned that alemtuzumab was an important comparator but was not included in the analysis. Accordingly, the committee agreed that none of the analyses presented for these subgroups were suitable for decision-making. It concluded that it had not been presented with robust evidence to show that daclizumab was cost effective in these subgroups.

Innovation

4.28 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. The

committee heard from the clinical experts that daclizumab does not represent a step-change in multiple sclerosis treatment in terms of either efficacy or safety profile. The committee concluded that it had not been presented with any evidence of additional benefits of daclizumab that were not captured in the QALYs.

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.

Committee conclusions

4.30 The committee concluded that daclizumab was not cost effective for patients without more active disease, whether they had previously had treatment or not (see section 4.26). The committee also concluded that it had not been presented with robust evidence that daclizumab was cost effective for people with more active disease (rapidly-evolving severe disease or highly active disease despite previous treatment) (see section 4.26). Because the committee considered the analyses to be highly uncertain or not relevant to the NHS, it invited the company to submit revised analyses for each subgroup, including the committee's preferred assumptions:

- using a revised mixed treatment comparison with the DECIDE subgroup data and including alemtuzumab as a comparator (see sections 4.11–4.13)

- using confirmed disability progression sustained for 6 months as the outcome measure when there are data for all comparators, but otherwise using 3-month data (see section 4.9)
- assuming quicker progression to higher EDSS states for people with rapidly-evolving severe disease or highly active disease despite previous treatment (see section 4.22)
- including a treatment waning effect (see section 4.14)
- assuming 12 doses of daclizumab per year (see section 4.18)
- including up to 4 doses of alemtuzumab in total (see section 4.19)
- omitting the half-cycle correction for alemtuzumab costs (see section 4.19)
- using the 3-year data to extrapolate stopping rates with daclizumab (see section 4.16)
- using costs that are in line with the NICE reference case (see section 4.21).

The committee would prefer probabilistic analyses, and would like the company to present both pairwise and fully incremental analyses.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Daclizumab for treating relapsing–remitting multiple sclerosis**	**Section**
Key conclusion		
Daclizumab is not recommended within its marketing authorisation for treating relapsing forms of multiple sclerosis in adults. Daclizumab reduced the annualised relapse rate and confirmed disability progression compared with placebo and interferon beta-1a (Avonex) in the overall trial population. However, the clinical-effectiveness results for subgroups were very uncertain. This was because the subgroups were based on small numbers, and		1.1 4.10

alemtuzumab (a key comparator) was not included in any of the subgroup mixed treatment comparisons. There was a very high degree of uncertainty associated with the cost-effectiveness modelling for daclizumab. This was because of the weaknesses in the mixed treatment comparisons and the lack of comparisons with alemtuzumab for any of the subgroups.		4.23
Current practice		
Clinical need of patients, including the availability of alternative treatments	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. People switching to a different therapy for efficacy reasons are usually offered dimethyl fumarate, teriflunomide or alemtuzumab. 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.	4.3 4.4
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Daclizumab statistically significantly reduces the annualised relapse rate and confirmed disability progression compared with placebo and interferon beta-1a. Patient experts advised that daclizumab's monthly subcutaneous injection regimen reduced unpleasant injection-related side effects and caused less disruption to daily routines. Clinical experts advised that daclizumab does not represent a step change in either efficacy or safety.	4.10 4.28
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 placebo (n=621); and DECIDE, a phase III study in which patients had treatment with	4.7

	daclizumab or interferon beta-1a (n=1,841).	
Relevance to general clinical practice in the NHS	The DECIDE and SELECT trials recruited patients who had had at least 1 relapse in the previous year. This differs from previous NICE guidance, which recommends that people have treatment with a disease-modifying therapy if they experience at least 2 relapses in the previous 2 years.	4.8

Uncertainties generated by the evidence	The SELECT trial was used for most of the subgroup mixed treatment comparisons and therefore the subgroup modelling. However, for some subgroups, the number of patients was very small, making the results very uncertain. The committee would have preferred the larger DECIDE trial to have been used in the mixed treatment comparisons.	4.11, 4.13
	Alemtuzumab is an important comparator and was specified in the NICE scope for each subgroup. However, the company's mixed treatment comparison could not link trials containing alemtuzumab to any of the subgroup evidence networks. The committee concluded that it could not make a decision about the cost effectiveness of daclizumab without considering comparisons with alemtuzumab.	4.12
	The company presented results based on confirmed disability progression sustained for 3 months. The committee preferred confirmed disability progression sustained for 6 months because people may still recover from a relapse after 3 months. However, the committee noted that specifying disability progression sustained for 6 months excluded some comparators from the mixed treatment comparison and model. It concluded that 6-month data should be used when available for all comparators in a subgroup; otherwise 3-month data should be used.	4.9

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The clinical-effectiveness results for subgroups were very uncertain. This was because the clinical data came from a small numbers of patients, and alemtuzumab (a key comparator) could not be included in any subgroup mixed treatment comparison.	4.11, 4.12
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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). 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 mixed treatment comparisons were very uncertain.	4.10, 4.11
Evidence for cost effectiveness		
Availability and nature of evidence	The company submitted an economic model that was structurally similar to other models used in previous NICE technology appraisals.	4.15

Uncertainties around and plausibility of assumptions and inputs in the economic model	The model assumed that patients progressed to higher expanded disability status scale (EDSS) health states at the same rate, irrespective of whether they had moderate or high disease activity. The committee would prefer to see analyses in which the subgroups with more active disease progressed to higher EDSS states at a quicker rate than the subgroups with less active disease. The annual health-state costs used by the company included some non-reference case costs, such as informal care. However, the evidence review group's (ERG's) preferred costs were substantially lower than costs that had been used in previous appraisals. The committee invited the company to submit revised cost estimates, excluding non-NHS and personal social services costs. The committee also asked the company to compare its cost estimates with the costs used in previous appraisals and explain any substantial differences	4.22 4.21

Incorporation of health-related quality-of-life benefits and utility values 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?	Patient experts advised that daclizumab's monthly subcutaneous injection regimen reduced unpleasant injection-related side effects and caused less disruption to daily routines. The committee noted that other treatments for multiple sclerosis also offer these benefits. 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.	4.2, 4.28
Are there specific groups of people for whom the technology is particularly cost effective?	The committee concluded that daclizumab was not cost effective in people without more active disease whether they had had treatment or not. In the 2 subgroups of people with more active disease, the committee was not presented with analyses suitable for decision-making.	4.26 4.27
What are the key drivers of cost effectiveness?	• Hazard ratios for disability progression • Health-state costs	4.10 4.11 4.21

Most likely cost-effectiveness estimate (given as an ICER)	The committee could not identify a most plausible incremental cost-effectiveness ratio because of the significant uncertainties in the cost-effectiveness modelling.	4.26, 4.27
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.	4.25
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 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
September 2016

6 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
Technical Adviser

Jeremy Powell

Project Manager

ISBN: [to be added at publication]