Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Technology appraisal guidance
Published: 28 September 2016
nice.org.uk/guidance/ta407
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Recommendations

1.1 Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

1.2 Assess the response to secukinumab after 16 weeks of treatment and only continue if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50\% of the pre-treatment value or by 2 or more units and

- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

1.3 When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.
## The technology

<table>
<thead>
<tr>
<th><strong>Description of the technology</strong></th>
<th>Secukinumab (Cosentyx, Novartis). It is a monoclonal antihuman antibody of the IgG1/kappa isotype that targets interleukin-17A.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marketing authorisation</strong></td>
<td>Secukinumab has a marketing authorisation in the UK for the treatment of active ankylosing spondylitis ‘in adults who have responded inadequately to conventional therapy’.</td>
</tr>
<tr>
<td><strong>Adverse reactions</strong></td>
<td>The overall incidence of treatment-emergent adverse events up to week 16 in the MEASURE 2 trial was comparable between the secukinumab 150-mg group (65.3%) and the placebo group (63.5%). In MEASURE 1 there was a higher rate in the secukinumab 150-mg group than with placebo (69.6% compared with 55.7%). There were no treatment-related deaths. For full details of adverse reactions and contraindications, see the summary of product characteristics.</td>
</tr>
<tr>
<td><strong>Recommended dose and schedule</strong></td>
<td>The recommended dose is 150 mg once weekly given by subcutaneous injection at weeks 0, 1, 2 and 3; followed by a maintenance dose once a month starting at week 4.</td>
</tr>
<tr>
<td><strong>Price</strong></td>
<td>Secukinumab is available at the list price of £609.39 for a 150-mg pre-filled pen or syringe (excluding VAT, ‘British national formulary’ [BNF] July 2016). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of secukinumab, 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.</td>
</tr>
</tbody>
</table>
3 Evidence

The appraisal committee (section 6) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). It also considered evidence received from patient and professional groups. See the committee papers for full details of the evidence.
4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of secukinumab, having considered evidence on the nature of ankylosing spondylitis (AS) and the value placed on the benefits of secukinumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The committee discussed the clinical-effectiveness evidence presented by the company, its critique by the evidence review group (ERG) and evidence submitted by patient and professional groups. The clinical-effectiveness evidence for secukinumab is in the company's submission (pages 42–155) and in the ERG report (pages 33–87).

Current clinical management of active ankylosing spondylitis

4.2 The clinical experts stated that the response criteria used in NICE's technology appraisal on TNF-alpha inhibitors for AS – that is, a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units, and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more – are used in clinical practice and are relevant to the appraisal of secukinumab in active AS.

4.3 People with AS may have additional non-spinal manifestations of disease such as uveitis, colitis, psoriasis, and peripheral arthritis. TNF-alpha inhibitors have different effects on extra-articular manifestations and so the choice of TNF-alpha inhibitor in clinical practice is based on individual patient characteristics and guided by any additional indications included in the marketing authorisation. Secukinumab has a licence for, and is recommended in NICE's technology appraisal guidance on, secukinumab for the treatment of moderate to severe plaque psoriasis. It also has a licence for psoriatic arthritis and is the subject of an ongoing NICE technology appraisal. The committee understood that the choice of agent for treating AS is made on an individual patient basis, based on disease characteristics and extra-articular symptoms.

4.4 The committee noted that a patient organisation submission included a survey of several hundred patients with AS, which summarised the major effect that the disease has on people's health and quality of life. The committee heard that
having a greater choice of treatments would be particularly valuable to people with this condition, allowing them and their clinicians to choose treatments that take into account their individual needs and preferences and giving them a feeling of more control over their condition. The clinical experts stated that the novel mechanism of action of secukinumab, and its other marketing authorisations for psoriasis and psoriatic arthritis, would give patients and clinicians a greater choice of targeted treatment options. A patient expert stated that it is particularly important to have the option of a treatment with a different mechanism of action for patients whose disease did not respond to one or more TNF-alpha inhibitors. The committee concluded that the availability of an effective new treatment option would be valuable for people with active AS.

The evidence from the MEASURE trials

4.5 The MEASURE 1 and MEASURE 2 trials, which compared secukinumab with placebo in active AS, were conducted across international sites. The committee expressed concern that concomitant treatments, which were not used in trials for TNF-alpha inhibitors (such as methotrexate and sulfasalazine), might have affected the results of the trials and their generalisability to UK clinical practice. The clinical experts stated that non-biological agents such as methotrexate and sulfasalazine have no proven activity in spinal disease but may be prescribed for extra-articular manifestations. The committee noted that MEASURE 1 and MEASURE 2 did not assess the effect of treatments on extra-articular manifestations, only the effects on AS. It also considered whether the results of MEASURE 1 were relevant to the use of subcutaneously administered secukinumab in UK clinical practice, as an intravenously administered dose was used up to week 4 (at week 8 and every subsequent 4 weeks secukinumab was administered subcutaneously), not reflecting the regimen which was subsequently licensed. The clinical experts stated that the magnitude of response in both studies was similar despite the differences between them in administration and loading dose. The committee concluded that the results from MEASURE 1 and MEASURE 2 were comparable and generalisable to the UK population.

4.6 The primary outcome measure in the MEASURE trials was the proportion of patients who had an Assessment in Spondyloarthritis International Society (ASAS) 20 response at week 16. The proportion of patients whose Bath
Ankylosing Spondylitis Disease Activity Index (BASDAI) score improved by 50% from baseline, and also the change in Bath Ankylosing Spondylitis Functional Index (BASFI) score from baseline, were collected as secondary endpoints. The committee noted that the MEASURE 1 and 2 trials assessed patients at 16 weeks (in accordance with the marketing authorisation) rather than 12 weeks, which is the standard assessment point used for TNF-alpha inhibitors (see NICE’s technology appraisal guidance on TNF-alpha inhibitors for AS). The clinical experts stated that patients on TNF-alpha inhibitors are routinely assessed at 12 weeks as recommended in the guidance. However, if a patient had a partial response to treatment at 12 weeks clinicians might continue TNF-alpha inhibitor treatment and reassess at 6 months.

4.7 The MEASURE trials demonstrated statistically significant improvements in ASAS 20 for secukinumab; 60.8% (odds ratio [OR] 3.89, 95% confidence interval [CI] 2.28 to 6.65, p<0.05) in MEASURE 1, and 61.1% (OR 4.38, 95% CI 2.14 to 8.96, p<0.05) in MEASURE 2, compared with 28.7% and 28.4% for placebo respectively. There were also statistically significant improvements in the BASDAI 50 (the proportion of patients achieving a 50% improvement in BASDAI score) and in the change from baseline BASFI scores in the secukinumab arms of the trials compared with placebo. The committee noted, and the clinical experts confirmed, that the magnitude of response in the MEASURE trials was broadly stable between 12 and 16 weeks. The committee concluded that the outcome measures used in the trials were appropriate, and that the 16-week assessment of response was in line with the marketing authorisation, and acceptable for decision making. The committee concluded that secukinumab was associated with a statistically significant improvement, compared with placebo, for the disease outcomes included in MEASURE 1 and 2.

Adverse effects

4.8 In MEASURE 1 there was a higher rate of treatment-emergent adverse events in the secukinumab 150-mg group than in the placebo group (69.6% compared with 55.7%). But in MEASURE 2 the overall incidence of adverse events in the secukinumab 150-mg group (65.3%) was comparable to placebo (63.5%). Nasopharyngitis was the most frequently reported adverse event in both trials and was observed more often in the secukinumab groups than in the placebo
groups of the trials. The committee concluded that the adverse effect profile of secukinumab is acceptable.

The company’s network meta-analysis

4.9 The company did a network meta-analysis to estimate the relative effectiveness of secukinumab 150 mg and the relevant comparator therapies in a mixed population of patients with AS that had been treated with a biologic agent before (biologic-experienced) or had not (biologic-naive), with a subgroup analysis in the biologic-naive population only. The committee noted that the marketing authorisations for the TNF-alpha inhibitors are for 'active severe AS' and the marketing authorisation for secukinumab is for 'active AS'. However the clinical experts explained that the inclusion criteria for severity in all the clinical trials was a BASDAI score equal to or greater than 4, and so all the treatments had been compared in a similar population.

4.10 The company's base-case analysis was based on the time of primary endpoint assessment for each treatment, which was week 12 for the TNF-alpha inhibitors and week 16 for secukinumab. The data from both the MEASURE trials was pooled for secukinumab. The clinical experts advised that because the magnitude of response was similar in MEASURE 1 and 2, it was reasonable for the company to include them both in its meta-analysis. The company's mixed-treatment comparison showed higher efficacy for secukinumab 150 mg compared with placebo across all outcomes for the whole population and also for the biologic-naive subgroup, with similar efficacy in both populations. The committee concluded that secukinumab has a similar efficacy to the TNF-alpha inhibitors.

Cost effectiveness

4.11 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. The cost-effectiveness evidence is in the company's submission (pages 156–239), in the company's response to clarification and in the ERG report (pages 88–186).

The company’s model

4.12 The company based its model's structure on the York model developed for NICE's technology appraisal guidance on TNF-alpha inhibitors for AS. The
committee noted that the York model had been criticised by the committee for that appraisal for the manner in which the response rates and absolute change from baseline at the end of the induction period were derived independently from evidence synthesis. The committee acknowledged the ERG's comment that an alternative model, such as patient-level simulation, could have been used. This would have reflected patient heterogeneity, the dependence between baseline BASDAI and BASFI values, the change from baseline values and response rates at the end of the induction period. However, the committee concluded that for the purposes of this appraisal, the broad principles of the York model were appropriate.

4.13 The company's base-case cost-effectiveness analysis, for the biologic-naive population, took into account the patient access schemes for secukinumab, golimumab and certolizumab pegol. The committee noted that:

- secukinumab had the lowest acquisition and administration costs and was associated with more quality-adjusted life years (QALYs) than most of the TNF-alpha inhibitors.
- in all of the scenarios explored by the company, secukinumab was the least expensive treatment compared with all the TNF-alpha inhibitors (see table 107 of the company's submission for more details).

4.14 The company's base-case cost-effectiveness analysis for the biologic-experienced population also took into account the patient access scheme for secukinumab. The incremental cost-effectiveness ratio (ICER) for secukinumab compared to conventional care was £2,245 per QALY gained for the biologic-experienced population.

The ERG's analyses

4.15 The ERG's exploratory analyses used a network meta-analysis, including secukinumab data from both MEASURE 1 and MEASURE 2, assessing response at week 12 instead of week 16, and using a standard withdrawal rate for all treatments as in the York model. The results of the ERG's exploratory base case were similar to the company’s in that secukinumab remained the least expensive treatment, although the QALYs gained (9.185) were lower than in the company's base-case analysis (9.805) and were also lower than most TNF-alpha inhibitors except etanercept and its biosimilars. The committee noted that the ICERs for the TNF-alpha inhibitors compared with secukinumab ranged from
approximately £38,800 to £71,600 per QALY gained, which is outside the range that is normally considered to be a cost-effective use of NHS resources.

4.16 The ERG's additional scenario analyses tested structural uncertainties in the assumptions in the base case. The committee noted that in the biologic-naïve population, secukinumab dominates etanercept (both original and biosimilar version); that is, it results in more QALYs and lower costs in all scenarios. Infliximab (both original and biosimilar version at list price) is associated with higher QALYs and higher costs than secukinumab. Adalimumab, golimumab and certolizumab pegol are mostly associated with higher QALYs and higher costs than secukinumab. For the scenarios in which different treatment effectiveness inputs were used (for example, from different network meta-analyses), secukinumab dominates these treatments; that is, secukinumab provides higher QALYs with lower costs. In the biologic-experienced population, in almost all of the ERG’s scenario analyses, secukinumab was associated with higher QALYs and higher costs, with ICER values below £20,000 per QALY.

The committee's conclusions

4.17 Based on the analyses presented by the company and ERG, the committee concluded that secukinumab was less expensive and resulted in a similar number of QALYs to the TNF-alpha inhibitors in people with AS that had not been treated with a biologic agent before. The committee concluded that secukinumab could be considered a cost-effective use of NHS resources for people with AS that has not been previously treated with TNF-alpha inhibitors.

4.18 In the biologic-experienced population, the committee noted that the ICER for secukinumab compared to conventional care was £2,245 per QALY gained in the company base case and was similar in the ERG’s exploratory base case (£2,223 per QALY gained). The committee concluded that secukinumab could be considered a cost-effective use of NHS resources for people with AS that has been previously treated with TNF-alpha inhibitors.

Innovation

4.19 The company stated that secukinumab is innovative and a step change in the management of active AS, because it is the first in its class and differs in its mechanism of action from existing treatments. The committee accepted that secukinumab is a promising new advance in treating people with active AS. The
committee concluded that secukinumab could be considered an innovative new treatment for the treatment of active AS but did not identify any quantifiable additional effects which had not been taken into account in the calculation of cost effectiveness.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.20 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 there is any basis for taking a different view about the relevance of the PPRS to 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

<table>
<thead>
<tr>
<th>TA407</th>
<th>Appraisal title: Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors</th>
<th>Section</th>
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</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td>Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis (AS) in adults whose disease has responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme. The committee concluded that secukinumab could be considered a cost-effective use of NHS resources for people with AS that has, or has not, been previously treated with TNF-alpha inhibitors.</td>
<td>1.1, 4.17, 4.18</td>
</tr>
<tr>
<td>Current practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical need of patients, including the availability of alternative treatments</td>
<td>The committee understood the important role of TNF-alpha inhibitors in the management of AS and that the choice of agent is made on an individual patient basis, based on disease characteristics and extra-articular symptoms (non-spinal manifestations of disease). The committee concluded that the availability of an effective new treatment option would be valuable for people with active AS.</td>
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</tbody>
</table>

**The technology**

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>Secukinumab is the first in its class of interleukin-17A inhibitors and has a different mechanism of action than the TNF-alpha inhibitors. The committee accepted that secukinumab is a promising new advance and could be considered an innovative new treatment for the treatment of active AS.</th>
</tr>
</thead>
</table>

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<thead>
<tr>
<th>What is the position of the treatment in the pathway of care for the condition?</th>
<th>The committee concluded that secukinumab could be considered an effective new treatment option for people with AS that has, or has not, been previously treated with TNF-alpha inhibitors.</th>
</tr>
</thead>
</table>

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<tr>
<th>Adverse reactions</th>
<th>In the MEASURE 1 trial there was a higher rate of treatment-emergent adverse events in the secukinumab 150-mg group than in the placebo group. But in MEASURE 2, the overall incidence of adverse events in the secukinumab group was comparable to placebo. The committee concluded that the adverse effect profile of secukinumab is acceptable.</th>
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</thead>
</table>

**Evidence for clinical effectiveness**

<table>
<thead>
<tr>
<th>Availability, nature and quality of evidence</th>
<th>The MEASURE 1 and MEASURE 2 trials compared secukinumab with placebo in active AS, and were conducted across international sites.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>The committee concluded that the results from MEASURE 1 and MEASURE 2 were comparable and generalisable to the UK population.</td>
</tr>
<tr>
<td>Uncertainties generated by the evidence</td>
<td>The committee expressed concern that concomitant treatments, which were not used in trials for TNF-alpha inhibitors, might have affected the results of the trials. It also considered whether the results of MEASURE 1 were relevant to the use of subcutaneously administered secukinumab in UK clinical practice as an intravenously administered dose was used up to week 8, not reflecting the regimen which was subsequently licensed. The committee concluded that the results from MEASURE 1 and MEASURE 2 were comparable and generalisable to the UK population.</td>
</tr>
<tr>
<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
<td>–</td>
</tr>
</tbody>
</table>
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The committee concluded that secukinumab was associated with a statistically significant improvement, compared with placebo, for the disease outcomes included in MEASURE 1 and MEASURE 2.
The company’s mixed-treatment comparison showed higher efficacy for secukinumab 150 mg compared with placebo across all outcomes for the whole population and also for the biologic-naïve subgroup, with similar efficacy in both populations. The committee concluded that secukinumab has a similar efficacy to the TNF-alpha inhibitors. | 4.7, 4.10 |

Evidence for cost effectiveness
<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The company based its model's structure on the York model developed for NICE's technology appraisal guidance on TNF-alpha inhibitors for AS. The committee concluded that for the purposes of this appraisal, the broad principles of the York model were appropriate.</th>
<th>4.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
<td>The committee noted that the York model had been criticised for the manner in which the response rates and absolute change from baseline at the end of the induction period were derived independently from evidence synthesis.</td>
<td>4.12</td>
</tr>
<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The company based its model's structure on the York model developed for NICE's technology appraisal on TNF-alpha inhibitors for AS in which the response rates and absolute change from baseline at the end of the induction period were derived independently from evidence synthesis.</td>
<td>4.12</td>
</tr>
<tr>
<td>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?</td>
<td>There are no specific groups of people with active AS for whom secukinumab is particularly cost effective.</td>
<td>-</td>
</tr>
</tbody>
</table>
What are the key drivers of cost effectiveness?
The cost of secukinumab and the choice of network meta-analysis. 4.13, 4.15

Most likely cost-effectiveness estimate (given as an ICER)
Based on the analyses presented by the company and ERG, the committee concluded that secukinumab was less expensive and resulted in a similar number of QALYs to the TNF-alpha inhibitors in people with AS that had not been treated with a biologic agent before.
In the biologic-experienced population, the committee noted that the ICER for secukinumab compared to conventional care was £2,245 per QALY gained in the company base case and was similar in the ERG’s exploratory base case (£2,223 per QALY gained). 4.17, 4.18

Additional factors taken into account

| Patient access schemes (PPRS) | The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of secukinumab, 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. |
| End-of-life considerations | – |
| Equalities considerations and social value judgements | None. |
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 active ankylosing spondylitis and the doctor responsible for their care thinks that secukinumab is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.4 The Department of Health and Novartis have agreed that secukinumab 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 the Commercial Operations Team at Novartis Pharmaceuticals UK on 01276 698717 or email commercial.team@novartis.com.
6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A. The technology appraisal committees are standing advisory committees of NICE.

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.

Richard Diaz and Victoria Kelly
Technical Leads

Eleanor Donegan
Technical Adviser

Marcia Miller and Liv Gualda
Project Managers

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Accreditation

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