



**Cytisnicline for Smoking Cessation  
Response to Public Comments on Draft Evidence Report**

**DECEMBER 11, 2025**

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<b>Manufacturer</b>		
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1.	ICER appropriately recognizes cytisinicline’s improved efficacy over behavioral support alone. And we agree with ICER that safety and tolerability with cytisinicline, particularly the lower rate of gastrointestinal side effects such as nausea, is differentiating over varenicline. We commend ICER on its patient-centric positioning that many more smokers who are motivated to quit can be helped with cytisinicline.	Thank you for your comments.
2.	Further, as you are aware, QALY or evLY measurements have many detractors, including payers, because those measures are long-term vs. short-term value indicators. However, the payer community recognizes – as does the public health community – the value of prevention and the robust existing evidence that links smoking to diseases such as CVD, COPD, and lung cancer.	The QALY and evLY can be used as both a long-term and short-term measure of benefit in the economic model. The results of both measures were presented alongside clinical outcomes including cases of COPD, lung cancer, and cardiovascular disease events for each intervention.
3.	<b>Cytisinicline is a new chemical entity</b> – Throughout the Draft Evidence Report, reference is made to comparators using studies that reviewed the efficacy of cytisine for smoking cessation. As we pointed out when submitting our comments to ICER’s Draft Scoping Document in June, cytisinicline and the older ex-U.S. cytisine products are different and distinct treatments. The FDA considers cytisinicline as a “new chemical entity” (NCE). An NCE is “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, or has been previously marketed as a drug in the U.S. Achieve Life Sciences (Achieve) filed an Investigational New Drug (IND) application in 2017 for developing cytisinicline as a new treatment for nicotine dependence and recently filed a New Drug Application (NDA) with the FDA. Ex-U.S., cytisine is given in a complex 25-day treatment regimen with the dosage starting at six 1.5 mg tablets daily for the	<b>It is our understanding that cytisinicline and cytisine are the same chemical entity.</b>  On the FDA web page that displays the chemical structure of cytisinicline they list cytisine as one of the “Names and synonyms” for this chemical entity:  <a href="https://precision.fda.gov/ginas/app/ui/substances/3c111fb7-2784-487c-84fd-3b08e5537e31">https://precision.fda.gov/ginas/app/ui/substances/3c111fb7-2784-487c-84fd-3b08e5537e31</a>  Furthermore, all the experts in the field we spoke with told us that the chemicals were the same.  This chemical has been used for smoking cessation in Europe since the 1960s. We were careful in the report to highlight the differences in the dosing schedules, and we did not include the earlier dosing schedule in the network meta-analyses (NMA) that informed our review and economic analyses.

	<p>first three days, then with a specific reduction schedule over three weeks ending with one 1.5 mg dosage on the last day. In trials, Achieve has optimized cytisinicline treatment using a novel tablet dosing, revised schedule, and longer treatment durations: a 3 mg tablet formulation given orally three times per day (TID) for 6 or 12 weeks. The formulation, dosage and duration of treatment are unique to cytisinicline. Cytisinicline used in the Achieve Life Sciences product is being manufactured under strict GMP standards required for distribution and use in the U.S. with additional purification not present in the manufacture of cytisine. In short, the Achieve-developed cytisinicline product is distinct from the older ex-U.S. cytisine product, and the Draft Evidence Report should treat it accordingly.</p>	
4.	<p><b>Reliance on 2023 Cochrane Review –</b> Throughout the Draft Evidence Report, ICER reviewers rely on the 2023 Cochrane review, <i>Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses</i>. The Cochrane meta-analysis compares cytisine with varenicline and other interventions. As noted above, cytisine and cytisinicline are different chemical entities, with novel formulation, dosing, schedules, and treatment durations. It is inappropriate, therefore, to base any conclusions regarding the efficacy of cytisinicline versus varenicline or other therapies on this Cochrane review. We suggest relying instead on the Phase 3 cytisinicline data from ORCA-2 and ORCA-3 and odds ratios referenced below.</p>	<p>This assertion is <b>false</b>. For our primary comparisons between cytisinicline, varenicline, and behavioral support alone, we only used data from the ORCA-2 and ORCA-3 trials, and we performed our own NMA, which did not include trials of the traditional dosing regimen for cytisine/cytisinicline. The results used in the economic modeling came from our NMA and did not come from the 2023 Cochrane review. The primary focus of our review was on the new dosing schedule that forms the basis of the current FDA submission. The Cochrane meta-analysis played <b>no role</b> in our primary comparative clinical effectiveness evaluations nor in our economic analyses.</p> <p>For the secondary comparisons (not part of the economic modeling), we did use the results from the 2023 Cochrane meta-analysis. And as noted above, cytisine and cytisinicline are identical chemical entities. According to the FDA, they are synonymous.</p>
5.	<p><b>Odds Ratios</b> As the Draft Evidence Report notes, in two large Phase 3 trials (ORCA-2 and ORCA-3), cytisinicline treatment regimens for 6 or 12 weeks were significantly more effective than placebo treatment with standard behavioral support in achieving long-term (through Week 24) smoking cessation success as demonstrated by odds ratios (ORs) below.</p> <ul style="list-style-type: none"> <li>• ORCA-2: At Week 24, continuous abstinence rates remained significantly</li> </ul>	<p>Thank you for your comment.</p> <p>As you are aware, the odds ratio exaggerates the effect size when the outcome is common as it is with smoking cessation as reported in the ORCA-2 and ORCA-3 trials. As you note, there are no head to head comparisons of cytisinicline and varenicline, so indirect comparisons are required to assess the comparative effectiveness. For our NMA, we just included data from the ORCA-2 and ORCA-3 trials, but as risk ratios so as to account for differences in the placebo response rate across the included trials.</p>

<p>higher than placebo plus behavioral support for:</p> <ul style="list-style-type: none"><li>- 6-weeks: abstinence from Week 3 to 24: OR 3.7 (95% CI, 1.5–10.2; P = .002);</li><li>- 12-weeks: abstinence from Week 9 to 24: OR 5.3 (95% CI, 2.8–11.1; P &lt; .001)</li><li>• ORCA-3: Replicated these findings with:<ul style="list-style-type: none"><li>- 6-weeks: abstinence from Week 3 to 24: OR 6.3 (95% CI, 1.9–34.6; P &lt; .001);</li><li>- 12-weeks: abstinence from Week 9 to 24: OR 5.8 (95% CI, 2.9–12.4; P &lt; .001)</li></ul></li></ul> <p>While no direct head-to-head trial comparisons have been conducted, the efficacy for cytisinicline in ORCA-2 and ORCA-3 (as demonstrated by ORs) was higher than what has been reported for other prescription therapies (Anthenelli, 2016) including varenicline (OR of 2.7 for Week 9 to 24 continuous abstinence) and bupropion (OR of 1.8 for Week 9 to 24 continuous abstinence). In addition, smokers who had previously unsuccessfully used both varenicline and bupropion to quit smoking achieved long-term smoking cessation through Week 24 when treated with cytisinicline for 6 or 12 weeks, compared to placebo with standard behavioral support.</p>	
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