

## 6.07 SECUKINUMAB,

**Solution for injection 300 mg in 2 mL pre-filled syringe,  
Solution for injection 150 mg in 1 mL pre-filled syringe,  
Solution for injection 150 mg in 1 mL pre-filled pen,  
Solution for injection 300 mg in 2 mL pre-filled pen,  
Cosentyx<sup>®</sup>,  
NOVARTIS PHARMACEUTICALS AUSTRALIA PTY LIMITED**

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule, Authority Required listing for secukinumab for the treatment of moderate to severe hidradenitis suppurativa (HS).
- 1.2 The basis for the submission was a claim of non-inferior comparative effectiveness and safety versus adalimumab, supported by an indirect treatment comparison (ITC) using placebo as the common comparator. The submission presented a cost-minimisation approach (CMA) to adalimumab. The key components of the clinical issue addressed by the submission are presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients with moderate to severe hidradenitis suppurativa
Intervention	Secukinumab (300 mg at week 0,1,2,3 and 4 followed by 300 mg every 4 weeks).
Comparator	Adalimumab (160 mg at day 1, 80 mg at day 15, followed by 40 mg every week/80 mg fortnightly from day 29).
Outcomes	Clinical response: proportion of patients meeting hidradenitis suppurativa response criteria (HiSCR50); change in safety and tolerability.
Clinical claim	In patients with moderate to severe hidradenitis suppurativa secukinumab is superior in terms of comparative effectiveness and inferior in terms of comparative safety compared with placebo. In patients with moderate to severe hidradenitis suppurativa secukinumab is non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety compared with adalimumab.

Source: Table 1.1, p25 of the submission.

### 2 Background

#### **Registration status**

- 2.1 TGA status at time of PBAC consideration: Not registered. The submission was made under TGA/PBAC Parallel Process. The Delegate's Overview was available at time of consideration.
- 2.2 Secukinumab is currently TGA indicated and PBS listed for adult patients with severe psoriasis, severe psoriatic arthritis and ankylosing spondylitis and non-radiographic axial spondyloarthritis.

### Previous PBAC consideration

2.3 Adalimumab is the only PBS subsidised biologic immune inhibitor for patients with moderate to severe HS.

## 3 Requested listing

3.1 For brevity reasons, an abridged version of the restriction is presented below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty*	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Initial treatment 1, 2 and balance of supply					
Secukinumab, 150 mg/mL injection, 2 x1 mL pen devices OR syringe	\$6,145.10	4	8	0	Cosentyx Novartis Pharmaceuticals
Secukinumab, 150 mg/mL injection, 2 x1 mL pen devices OR syringes	\$1,634.73	1	2	2	
Secukinumab, 300 mg/2mL injection, 2 mL pen device OR syringe	\$6,145.10	4	1	0	
Secukinumab, 300 mg/2mL injection, 2 mL pen device OR syringe	\$1,634.73	1	1	2	
Continuing treatment (continuing and grandfather)					
Secukinumab, 150 mg/mL injection, 2 x1 mL pen devices OR syringes	\$1,634.73	1	2	5	Cosentyx Novartis Pharmaceuticals
Secukinumab, 300 mg/2mL injection, 2 mL pen device OR syringes	\$1,634.73	1	1	5	

Source: Table 1.6, p35 of the submission.

\*The submission stated that should the PBAC recommend secukinumab for listing, the sponsor will work with the Department on the published and effective prices. All prices presented in the submission were calculated using the published price of adalimumab. Following the submission, the price of adalimumab reduced on 1 April 2023. Further discussion is presented in the economic analysis section.

<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
<b>Administrative Advice:</b> Subcutaneous injection
<b>Severity:</b> Moderate to severe
<b>Condition:</b> Hidradenitis suppurativa
<b>Treatment Phase:</b> Initial treatment 1, new patient
<b>Clinical criteria:</b>
Patient must have, at the time of application, a Hurley stage II or III grading with an abscess and inflammatory nodule (AN) count greater than or equal to 3,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have failed to achieve an adequate response to 2 courses of different antibiotics each for 3 months prior to initiation of PBS subsidised treatment with this drug for this condition; OR

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Patient must have had an adverse reaction to an antibiotic of a severity necessitating permanent treatment withdrawal resulting in the patient being unable to complete treatment with 2 different courses of antibiotics each for 3 months prior to initiation of PBS-subsidised treatment with this drug for this condition; OR
Patient must be contraindicated to treatment with an antibiotic due to an allergic reaction of a severity necessitating permanent treatment withdrawal resulting in the patient being unable to complete treatment with 2 different courses of antibiotics each for 3 months prior to initiation of PBS-subsidised treatment with this drug for this condition,
<b>AND</b>
The treatment must be limited to a maximum duration of 16 weeks.
<b>Treatment criteria:</b>
Must be treated by a dermatologist
<b>Population criteria:</b>
Adult patients
<b>Prescribing Instructions:</b> Assessment of disease severity must be no more than 1 month old at the time of application. An assessment of the patient's response to this recommencement course of treatment must be made following a minimum of 12 weeks of treatment. At the time of authority application the prescriber must request the first 4 weeks of treatment under this restriction; and weeks 5 to 16 of treatment under Initial treatment 1 – New patient or Initial treatment 2 – Recommencement of treatment – balance of supply

Source: Table 1.7, pp36-37 of the submission.

<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
<b>Administrative Advice:</b> Subcutaneous injection
<b>Severity:</b> Moderate to severe
<b>Condition:</b> Hidradenitis suppurativa
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have demonstrated a response to treatment with this drug for this condition.
<b>Prescribing Instructions:</b> For the first application for continuing treatment a Hidradenitis Suppurativa Clinical Response (HiSCR) assessment must be made following a minimum of 12 weeks of treatment. For subsequent continuing treatment a HiSCR assessment must be made every 24 weeks. The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and provided to the Department of Human Services no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion.

Source: Table 1.7, p38 of the submission.

- 3.2 The submission noted secukinumab is currently subject to a Special Pricing Arrangement, with the current effective price based on the relative weightings across all PBS listed indications.
- 3.3 The TGA Draft Product Information (PI) allows for 2 dose regimens in the maintenance phase of treatment of HS: 300 mg once every 2 weeks (Q2W) or 300 mg once every 4 weeks (Q4W), stating that “Some patients may derive an additional benefit from receiving 300 mg every 2 weeks”. The submission indicated the sponsor would like both doses to be used in Australia and no dosing restrictions were included in the proposed PBS restriction. It is unclear how patients who may benefit from the Q2W

regimen would be identified, noting it would require twice as many secukinumab doses compared to the Q4W regimen.

3.4 The requested restriction for secukinumab was inconsistent with the populations studied in the key secukinumab trials, including Study 2301 (SUNSHINE) and Study 2302 (SUNRISE):

- The key trials did not require patients to have failed to respond to prior antibiotics. However, the proposed restriction requires patients to have failed to achieve an adequate response to 2 different courses of antibiotics prior to initiation secukinumab. This is further discussed in paragraph 6.13 below.
- The key trials measured treatment response after 16 weeks. The proposed restriction allows for treatment response measurement to occur between weeks 12 and 16 weeks. If patients in Australian clinical practice are measured for response earlier than 16 weeks of treatment, then it is likely that fewer patients will be recorded as ‘responders’, and the efficacy described by the key trials may not be realised in practice; if the proposed restriction measured for response between weeks 16 and 20, this would ensure a minimum of 16 weeks treatment. Differing time periods to assess response to treatment for the purposes of continuing therapy are common among listings for biologic or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) for other indications.
- The key trials enrolled patients with  $\geq 5$  total abscess and nodule count, located in  $\geq 2$  distinct anatomic areas. The proposed restriction allows secukinumab to be prescribed when there are  $\geq 3$  total abscess or inflammatory nodule count.

3.5 The Pre-Sub-Committee Response (PSCR) stated the pivotal adalimumab studies previously relied upon by the PBAC required patients to have an inadequate response to prior antibiotics, but did not specify a requirement for two different courses. The PSCR also stated that data on the proportion with prior antibiotic use and reasons for discontinuation were not reported in the available material and further noted subgroup analyses based on two prior courses of antibiotics were not presented in the adalimumab public summary documents (PSDs). On that basis, the PSCR argued it was reasonable to consider secukinumab on the same ground as adalimumab was recommended, with the same PBS listing; or to reduce the requirement in PBS listings for HS to one prior course of antibiotics.

3.6 The sponsor proposed a grandfathering clause to allow trial patients as well as those enrolled in the patient familiarisation program and the compassionate use program to transition to reimbursed secukinumab upon PBS listing.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **4 Population and disease**

4.1 Hidradenitis suppurativa is a painful, chronic, recurrent, and debilitating inflammatory

skin condition of the pilosebaceous follicle with an underlying immune system imbalance that occurs in genetically predisposed individuals. Hidradenitis suppurativa typically presents with deep, inflammatory, painful lesions in apocrine gland-bearing parts of the body. The most common areas affected are the axillae, the groin, and the anogenital region (Fimmel and Zouboulis 2010, Jemec 2012). The disease has a substantial negative effect on the quality of life and significant psychological effects, with multiple studies confirming the impact is greater than that seen with other dermatologic diseases (Deckers and Kimball 2016). Patients with HS also often suffer from depression, social isolation, impaired sexual health and difficulty performing work duties (Deckers et al 2014, Janse et al 2017).

- 4.2 The proposed treatment algorithm suggests either secukinumab and adalimumab may be used in patients who fail at least 2 courses of different antibiotics, and if patients fail to achieve a response with one biologic immune inhibitor, they may try the other one. There is limited clinical evidence supporting the efficacy of a second biologic immune inhibitor in patients who failed to achieve a response to prior immune inhibitor therapy.
- 4.3 The submission's current treatment algorithm did not consider the options available for patients who fail to achieve a response with adalimumab, which include a range of surgical interventions (from local incisions and deroof procedures to wide excision and grafting), short-term steroids (an effective treatment for debilitating pain and acute flares), treatment of comorbidities and regular wound care.<sup>1</sup>
- 4.4 Secukinumab is an IL-17 inhibitor that works by binding to human IL-17A and neutralises the bioactivity of this cytokine. IL-17A is recognised as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated adalimumab as the main comparator as it is the only therapy currently PBS listed for treatment of moderate to severe HS.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The Sponsor requested a hearing for this item. The clinician discussed the level of underdiagnosis of HS in clinical practice and noted it is often mistaken for other dermatological conditions. The clinician also described the significant impact on

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<sup>1</sup> Vekic & Cains, 2017, Hidradenitis suppurativa – Management, comorbidities and monitoring. *Australian Family Physician*, Vol 46, Issue 8.

patients' quality of life, to the extent where some people with HS are unable to participate in society or form personal relationships because of the fear and impact of draining fistulae. The hearing also outlined the high need for alternatives as adalimumab was currently the only available biologic for HS and some patients lose response to adalimumab or are unable to use it due to contraindications or comorbidities.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (7) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from healthcare professionals noted the need for additional treatment options, the loss of efficacy with alternative treatments and the impact of HS on patients' quality of life. The comments from patients who have tried secukinumab for HS and their parents or caregivers noted that while it has not completely eliminated their symptoms, there have been few side effects and treatment has reduced the severity of their disease, leading to reduced need for surgeries and improved quality of life. The comments from patients who wish to try secukinumab noted their current treatments have had limited effectiveness and outlined their hope treatment will improve their quality of life.
- 6.3 The PBAC noted input from the Australasian College of Dermatologists supported the listing and highlighted the importance of an additional/alternative effective treatment for HS on the PBS.
- 6.4 The PBAC also noted the input from the Centre for Community Driven Research (CCDR), which provided a decision-maker brief, including patient stories sharing their experience with HS and treatment with SEC. The PBAC noted the patient stories further highlighted the severe impact of HS on quality of life, including the pain and other unpleasant symptoms associated with draining fistulae, leading people to withdraw from society because of the fear, embarrassment and stigma associated with their disease.

### ***Clinical trials***

- 6.5 The submission was based on two randomised trials comparing secukinumab to placebo (SUNSHINE, N=541 and SUNRISE, N=543) and four head-to-head trials comparing adalimumab to placebo (M10-467, N=154; PIONEER I, N=307; PIONEER II, N=326; SHARPS, N=206). The two secukinumab trials had the same design and patient population.
- 6.6 The PBAC has previously considered 3 of the adalimumab trials: M10-467, and PIONEER I and II (adalimumab PSD, November 2016). The primary outcome was defined as a 50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count: a hidradenitis suppurativa clinical response of at least 50% (HiSCR50). The outcome was measured at Week 16 in the secukinumab and M10-467 trials, and at Week 12 in the PIONEER

and SHARPS trials.

- 6.7 SHARPS was a Phase IV trial designed to evaluate the perioperative efficacy of adalimumab in patients with moderate to severe HS who required radical surgery in an axillary or inguinal region, and had 2 other anatomical regions affected, with 1 or more regions at Hurley stage II or III. Patients had efficacy evaluations performed at Week 12 (pre-operative) and Week 24 (post-operative).
- 6.8 Details of the trials presented in the submission are provided in Table 2.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
2301 (SUNSHINE)	A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNSHINE) (NCT03713619) <a href="https://clinicaltrials.gov/ct2/show/NCT03713619">https://clinicaltrials.gov/ct2/show/NCT03713619</a> Internal clinical study report (CAIN4572301)	Jan 2023  Nov 2022
2302 (SUNRISE)	A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNRISE) (NCT03713632) <a href="https://clinicaltrials.gov/ct2/show/NCT03713632">https://clinicaltrials.gov/ct2/show/NCT03713632</a> Internal clinical study report (CAIN4572302) Kimball A.B., et al. Study design and baseline characteristics of phase 3 studies of secukinumab (SUNSHINE and SUNRISE) in patients with moderate to severe hidradenitis suppurativa.	Oct 2022  Dec 2022 5th Annual Symposium on Hidradenitis Suppurativa Advances. Virtual conference ePoster 2022
SUNNY OLE (extension of 2301 and 2302)	Extension Study to Assess Effects of Non-interrupted Versus Interrupted and Long Term Treatment of Two Dose Regimes of Secukinumab in Subjects With Hidradenitis Suppurativa (NCT014179175) <a href="https://clinicaltrials.gov/ct2/show/NCT014179175">https://clinicaltrials.gov/ct2/show/NCT014179175</a>	Jul 2022
PIONEER I	Efficacy and Safety Study of Adalimumab in Treatment of Hidradenitis Suppurativa (NCT01468207) <a href="https://www.clinicaltrials.gov/ct2/show/NCT01468207">https://www.clinicaltrials.gov/ct2/show/NCT01468207</a> Kimball, A. B., et al. "Two phase 3 trials of adalimumab for hidradenitis suppurativa."	Jul 2021  <i>New England Journal of Medicine</i> 2016; 375(5): 422-434.
PIONEER II	Efficacy and Safety Study of Adalimumab in the Treatment of Hidradenitis Suppurativa (NCT01468233) <a href="https://www.clinicaltrials.gov/ct2/show/NCT01468233">https://www.clinicaltrials.gov/ct2/show/NCT01468233</a>	Jul 2021
PIONEER OLE	Open-label Study of the Safety and Efficacy of Adalimumab in the Treatment of Hidradenitis Suppurativa (NCT01635764) <a href="https://clinicaltrials.gov/ct2/show/NCT01635764">https://clinicaltrials.gov/ct2/show/NCT01635764</a> Kimball, A. B., et al. "Two phase 3 trials of adalimumab for hidradenitis suppurativa."	Jan 2018  <i>New England Journal of Medicine</i> 2016; 375(5): 422-434.
M10-467	Study of adalimumab in subjects with moderate to severe chronic hidradenitis suppurativa (NCT00918255) <a href="https://clinicaltrials.gov/ct2/show/NCT00918255">https://clinicaltrials.gov/ct2/show/NCT00918255</a> Kimball, A. B., et al. "Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: A parallel randomized trial."	May 2011  <i>Annals of Internal Medicine</i> 2012; 157(12): 846-855.
SHARPS	Safety and Efficacy of Humira (Adalimumab) for Hidradenitis Suppurativa (HS) Peri-Surgically (SHARPS Study) (NCT02808975) <a href="https://clinicaltrials.gov/ct2/show/NCT02808975">https://clinicaltrials.gov/ct2/show/NCT02808975</a> Bechara, F. G., et al. "Efficacy and Safety of Adalimumab in Conjunction With Surgery in Moderate to Severe Hidradenitis Suppurativa: the SHARPS Randomized Clinical Trial."	May 2020  <i>JAMA Surgery</i> 2021; 156(11): 1001-1009.

Source: Table 2.10, pp 49-54 of the submission.

For brevity reasons, only the pivotal trial publication is shown for the adalimumab studies above. Further information on publications associated with the adalimumab trials is available in the adalimumab PSD for severe HS (July 2016).

6.9 The key features of the direct randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Secukinumab versus placebo</b>					
SUNSHINE	541	R, DB 16 weeks with OLE up to Week 52	Some concerns	Hurley Stage II and III	HiSCR50 at Week 16 Disease flares AN change from baseline NRS30 DLQI
SUNRISE	543	R, DB 16 weeks with OLE up to Week 52	Some concerns	Hurley Stage II and III	HiSCR50 at Week 16 Disease flares AN change from baseline NRS30 DLQI
<b>Adalimumab versus placebo</b>					
M10-467	154	R, DB 16 weeks with OLE up to 52 weeks	Low	Hurley Stage I, II and III	HS-PGA score at Week 16
PIONEER I	307	R, DB 36 weeks with OLE up to Week 108	Low	Hurley Stage II and III	HiSCR50 at Week 12
PIONEER II	326	R, DB 36 weeks with OLE up to Week 108	Low	Hurley Stage II and III	HiSCR50 at Week 12
SHARPS	206	R, DB 12 weeks with post-surgery period up to Week 24	Low	Hurley Stage II and III	HiSCR50 at Week 12

Source: Table 2.13, p 61 of the submission.

AN= abscess and inflammatory nodule; DB = double blind; DLQI = Dermatology Life Quality Index; HiSCR50 = hidradenitis suppurativa clinical response of at least 50%; HS-PGA = hidradenitis suppurativa Physician Global Assessment; NRS= numeric rating scale; OLE = open label extension; R = randomised.

6.10 The two key secukinumab trials were considered to have a risk of attrition bias, due to their handling of incomplete outcome data. At the evaluation for primary outcome (Week 16), there were differences in missing data between secukinumab and placebo arms (8% versus 15% respectively). The key trials used a mixed effects logistic regression with multiple imputations (including corresponding baseline values, geographical region, Hurley stage, use of antibiotics and body weight as covariates) to adjust the observed results, and did not perform sensitivity analyses considering last observation carried forward or non-responder imputations. Compared to the observed data, this approach favoured secukinumab in three out of the four treatment arms of the key trials. In contrast, the adalimumab trials recorded primary outcomes on the intention-to-treat (ITT) populations, where unevaluated patients were recorded as non-responders, with multiple sensitivity analyses performed in the PIONEER studies.

## Comparative effectiveness

6.11 Key results from the SUNSHINE and SUNRISE trials are presented in the table below.

**Table 4: Primary and secondary results of the key secukinumab trials, Week 16**

Trial ID	Secukinumab n/m (%)	Placebo <sup>a</sup> n/m (%)	Odds ratio (95% CI)
<b>SUNSHINE</b>			
<b>HiSCR50</b>			
Secukinumab Q2W	81.5/181 (45.0)	60.7/180 (33.7)	<b>1.75 (1.12, 2.73)</b>
Secukinumab Q4W	75.2/180 (41.8)	60.7/180 (33.7)	1.48 (0.95, 2.32) <sup>d</sup>
<b>Flares</b>			
Secukinumab Q2W	27.8/181 (15.4)	52.2/180 (29.0)	<b>0.42 (0.25, 0.73)</b>
Secukinumab Q4W	41.7/180 (23.2)	52.2/180 (29.0)	0.71 (0.43, 1.17)
<b>AN change from baseline</b>	<b>Mean (SE)<sup>b</sup></b>	<b>Mean (SE)<sup>b</sup></b>	<b>LSM difference (95% CI)<sup>b</sup></b>
Secukinumab Q2W	-46.8 (3.33)	-24.3 (4.33)	<b>-23.05 (-33.90, -12.21)</b>
Secukinumab Q4W	-42.4 (4.01)	-24.3 (4.33)	-18.46 (-29.32, -7.60)
<b>SUNRISE</b>			
<b>HiSCR50</b>			
Secukinumab Q2W	76.2/180 (42.3)	57.1/183 (31.2)	<b>1.64 (1.05, 2.55)</b>
Secukinumab Q4W	83.1/180 (46.1)	57.1/183 (31.2)	<b>1.90 (1.22, 2.96)</b>
<b>Flares</b>			
Secukinumab Q2W	36.1/180 (20.1)	49.5/183 (27.0)	0.68 (0.41, 1.14)
Secukinumab Q4W	28.0/180 (15.6)	49.5/183 (27.0)	<b>0.49 (0.29, 0.84)<sup>e</sup></b>
<b>AN change from baseline</b>	<b>Mean (SE)<sup>b</sup></b>	<b>Mean (SE)<sup>b</sup></b>	<b>LSM difference (95% CI)<sup>b</sup></b>
Secukinumab Q2W	-39.3 (4.43)	-22.4 (4.84)	<b>-16.33 (-28.79, -3.88)</b>
Secukinumab Q4W	-45.5 (4.08)	-22.4 (4.84)	<b>-22.94 (-35.24, -10.63)</b>
<b>SUNRISE and SUNSHINE</b>			
<b>NRS30<sup>c</sup></b>			
Secukinumab Q2W	90.8/233 (38.9)	61.9/230 (26.9)	<b>1.80 (1.18, 2.74)</b>
Secukinumab Q4W	79.4/222 (35.8)	61.9/230 (26.9)	1.54 (1.00, 2.38)

Source: Table 2.30, p 92 of the submission.

AN= abscess and inflammatory nodule; CI= confidence interval; HiSCR50 = hidradenitis suppurativa clinical response of at least 50%; LSM= least squares mean; m= number of subjects evaluable through multiple imputations; n= number of subjects in group; NRS= numeric rating scale; OR= odds ratio; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SE=standard error.

<sup>a</sup> Placebo Q2W and Q4W arms were pooled together for the primary analyses.

<sup>b</sup> The mean is the pooled mean over 100 imputations. SE is the pooled standard error over 100 imputations. Covariates included in the model: treatment group, geographical region, Hurley stage, use of antibiotic, baseline body weight and baseline AN count.

<sup>c</sup> NRS30 data pooled from both SUNSHINE and SUNRISE, defined as at least 30% reduction and at least 2 unit reduction from baseline.

<sup>d</sup> This result had a p = 0.0418, which was not significant due to the hierarchical design of the trial.

**Bold** indicates a statistically significant result.

6.12 In the SUNSHINE trial, the secukinumab Q2W arm achieved a statistically significant difference compared to placebo in terms of HiSCR50, AN count and flares, with the Q4W arm demonstrating a numeric superiority which did not reach statistical significance. In SUNRISE, both arms achieved a statistically significant difference compared to placebo in terms of HiSCR50 and AN count, but only the Q4W arm demonstrated a statistically significant difference in terms of flares. Improvements in the NRS30 included data pooled from both SUNSHINE and SUNRISE, and was only statistically significant in the Q2W arm.

6.13 The SUNRISE and SUNSHINE trials did not record how many different antibiotics were used, nor whether patients had a successful response to prior antibiotics or biologic

therapies (such as adalimumab or infliximab), which may confound the efficacy data. In the key secukinumab trials, patients were stratified by whether they had at least one course of prior antibiotics (regardless of response); approximately 81% to 84% had at least one prior antibiotic course, and 20% to 26% had prior biologic therapies. These confounders may explain some of the heterogeneity observed between the key secukinumab trials, where HiSCR50 response rates in the individual trial placebo arms varied from 30.4% to 37.2%, compared to the more homogenous population of the adalimumab M10-467 and PIONEER trials, where inter-trial placebo response rates only varied from 25.6% to 27.6%.

- 6.14 The PSCR acknowledged prior failure of antibiotics was not a requirement to enter the pivotal secukinumab studies, however stated it was expected the majority of patients entering the study would have previously received systemic antibiotics at least during the period since diagnosis ( $\geq 1$  year). The PSCR also stated more than 80% of the studied population had prior exposure to systemic antibiotics, with ~60% discontinuing due to lack of efficacy, and ~10-13% due to lack of tolerability; in terms of prior biologic use, the PSCR reiterated 20-26% of patients in the pivotal studies had prior biologic therapy. The ESC considered this clarification was informative and provided some confidence the secukinumab trial population(s) may be generalisable to the PBS population, and therefore the observed trial results (versus placebo) may be applicable to the requested listing.
- 6.15 The HiSCR50 response rates were presented for the open label extension (OLE) up to Week 52. The submission claimed that approximately 75% to 80% of patients who achieved a HiSCR50 response at Week 16 maintained the response at Week 52. This interpretation was vulnerable to survivorship bias<sup>2</sup>, as it examined only the subset of the Week 16 responders who continued treatment up to Week 52, demonstrated in Table 5 below. A more appropriate interpretation is to consider the proportion of responders at Week 52 as a subset of patients who demonstrated a response at Week 16 (bottom two rows of the table below). Further, the results indicate a HiSCR50 response at two discrete time points, and do not consider how many patients may have transiently lost their HiSCR50 response and regained it by Week 52; under the proposed PBS restriction, if patients lose their HiSCR50 response, secukinumab therapy would be discontinued.

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<sup>2</sup> Survivorship bias refers to a type of sample selection bias that occurs when an interpretation mistakes a visible successful subgroup as the entire group.

**Table 5: Percentage of Week 16 HiSCR50 responders who were in response at Week 52**

	Secukinumab Q2W n/M (%)	Secukinumab Q4W n/M (%)
<b>Week 52 HiSCR50 responses as a proportion of the patients who continued treatment up to Week 52</b>		
SUNSHINE	44/58 (75.9)	42/52 (80.8)
SUNRISE	51/61 (83.6)	50/65 (76.9)
<b>Week 52 HiSCR50 responses as a proportion of Week 16 responders</b>		
SUNSHINE	44/78 (56.4)	42/69 (60.9)
SUNRISE	51/71 (71.8)	50/79 (63.2)

Source: Data extracted from Table 11-6, p 79 of Attachment 6\_CSR2301-52wk.pdf and Table 11-6, p 77 of Attachment 6\_CSR2302-52wk.pdf.

HiSCR50 = hidradenitis suppurativa clinical response of at least 50%; M = number of subjects evaluable at respective timepoints; n = number of subjects with observed response; Q2W = every 2 weeks; Q4W = every 4 weeks.

6.16 The submission proposed that secukinumab may be used prior to, or after, adalimumab. Subgroup data of patients who had prior biologic therapy showed little difference in response rates (at Week 16) between the secukinumab and placebo arms of the SUNSHINE trial (Table 6), with a numeric trend for greater benefit in the secukinumab arm compared to placebo in SUNRISE, noting that numbers were low in these unstratified subgroups which were not powered to detect a difference.

**Table 6: HiSCR50 responses in patients with prior biologic therapy in the key secukinumab trials, Week 16**

	Secukinumab n/M (%)	Placebo <sup>a</sup> n/M (%)	Odds ratio (95% CI)
<b>SUNSHINE</b>			
Secukinumab Q2W	14.4/44 (32.8)	13.0/46 (28.3)	1.27 (0.51, 3.19)
Secukinumab Q4W	12.9/39 (33.2)	13.0/46 (28.3)	1.28 (0.50, 3.29)
<b>SUNRISE</b>			
Secukinumab Q2W	15.2/36 (42.1)	12.7/48 (26.4)	2.01 (0.76, 5.30)
Secukinumab Q4W	18.5/42 (44.0)	12.7/48 (26.4)	2.27 (0.89, 5.78)

Source: Data extracted from Table 2.18, p 69 of the submission, and Table 14.2-7.1a of the SUNSHINE and SUNRISE CSRs, as provided by the sponsor.

CI = confidence interval; HiSCR50 = hidradenitis suppurativa clinical response of at least 50%; M = number of subjects evaluable through multiple imputations; n = number of subjects with observed response; Q2W = every 2 weeks; Q4W = every 4 weeks.

<sup>a</sup> Placebo Q2W and Q4W arms were pooled together for analyses.

Note: Results have been modified by the mixed effects logistic regression with multiple imputations analyses ratios.

6.17 Table 7 below. The ITC had substantial transitivity issues, arising from key differences in inclusion criteria, as follows:

- The adalimumab trials (except SHARPS) enrolled patients who had disease refractory to at least two different antibiotic courses, whilst the key secukinumab trials did not require patients to have failed a prior course of antibiotics. This means that the efficacy of secukinumab in patients who have failed two prior antibiotics courses was unclear.
- Patients in the adalimumab trials generally had a lower AN count and higher draining fistulae count compared the key secukinumab trials, as the adalimumab trials required patients to have  $\geq 3$  AN, while the secukinumab trials included patients with  $\geq 5$  AN. This favoured the apparent efficacy of secukinumab, as immune inhibitors have greater efficacy in patients with more inflammatory

nodules, and are less effective in treating draining fistulae.<sup>3</sup>

- An unreported number of patients enrolled in M10-467 had Hurley Stage I disease, which is milder than Hurley Stage II and III required for enrolment in the secukinumab and other adalimumab trials. The other adalimumab trials had a greater proportion of patients with Hurley Stage III disease compared with the key secukinumab trials. It is unclear whether these differences may have biased efficacy outcomes.

The SHARPS trial design and population were distinct from the other trials included in the ITC, as it was designed to evaluate the perioperative efficacy of adalimumab in patients with moderate to severe HS who required radical surgery in an axillary or inguinal region, and had 2 other anatomical regions affected, with 1 or more regions at Hurley stage II or III. The patient population of SHARPS had a lower inflammatory nodule count than the other trials, and a high draining fistulae count, which likely reduced the apparent efficacy of adalimumab. This difference can be seen when comparing the efficacy described by SHARPS with the other adalimumab trials, in Table 8 below.

**Table 7: Key disease characteristics of patients in the direct randomised trials**

Study Name	Treatment arm	N	Disease duration (Years)	Inflammatory nodule count	Abscess count	Draining fistulae count	Hurley stage III
			Mean±SD	Mean±SD	Mean±SD	Mean±SD	%
SUNSHINE	SEC Q2W	181	7.4±8.0	10.1±7.8	2.9±4.3	2.9±3.4	38.7
	SEC Q4W	180	6.6±6.7	9.9±7.6	2.7±4.0	2.5±3.5	35.0
	PBO	180	7.5±7.0	10.1±7.0	2.7±3.8	2.4±3.2	28.3
SUNRISE	SEC Q2W	180	7.1±7.0	10.0±7.7	3.9±5.4	3.0±3.6	45.6
	SEC Q4W	180	8.2±8.4	10.4±7.6	2.9±4.1	2.5±3.5	37.8
	PBO	183	7.0±6.7	9.6±6.8	3.2±5.0	2.6±3.2	38.3
M10-467 <sup>a</sup>	Adalimumab weekly	51	11.3±9.1	NR	1.6	5.6	29.4
	PBO	51	13.4±10.4	NR	1.8	3.4	29.4
PIONEER I	Adalimumab weekly	153	8.8	11.5±10.9	2.8±3.5	4.6±5.2	47.7
	PBO	154	9.4	11.6±13.9	2.7±3.7	3.8±4.4	47.4
PIONEER II	Adalimumab weekly	163	9.0	8.6±6.9	2.0±2.6	3.0±5.2	47.2
	PBO	163	9.9	9.4±9.6	2.4±3.3	3.0±4.1	45.4
SHARPS	Adalimumab weekly	103	11.7±10.5	7.9±5.5	2.4±3.7	3.6±4.0	49
	PBO	103	10.0±9.0	8.5±9.1	2.8±6.1	4.0±5.4	48

Source: Data extracted from Table 2.18, p 69 of the submission.

DLQI= dermatology life quality index; NR= not reported; PBO= placebo; Q2W= once every 2 weeks; Q4W =once every 4 weeks; SD= standard deviation; SEC= secukinumab.

<sup>a</sup> Only TGA approved dose were reported.

6.18 The submission’s ITC of the combined Q2W and Q4W groups from the secukinumab trials versus the adalimumab trials is presented in Table 8 below. The ITC showed no statistically significant difference but a numeric difference in favour of adalimumab when compared to secukinumab (OR=0.63, [95% CI: 0.40, 1.01]). As the 95% CI

<sup>3</sup> Bechara FG et al., (2021), Efficacy and Safety of Adalimumab in Conjunction With Surgery in Moderate to Severe Hidradenitis Suppurativa: The SHARPS Randomized Clinical Trial. *JAMA Surg.* Nov 1;156(11):1001-1009.

traversed 1, the submission concluded that secukinumab (either Q2W or Q4W) was non-inferior, in terms of efficacy, compared to adalimumab. This was not a reasonable interpretation of these results; the absence of a statistically significant difference does not necessarily mean the two treatments have non-inferior efficacy. The evaluation considered a more reasonable interpretation of the ITC is that secukinumab demonstrated a trend towards inferiority compared to adalimumab in terms of efficacy, however the comparison lacked the power to achieve statistical significance and interpretation of the results is further complicated by the lack of a nominated non-inferiority margin. As discussed above, the trial design and population of the SHARPS RCT is distinct from the other trials; if the SHARPS trial were removed from the ITC, then secukinumab treatment was statistically significantly inferior to adalimumab.

- 6.19 The PSCR argued the number of required ANs in the secukinumab trials assures that patients would meet the definition of moderate to severe disease in the HS-PGA tool. The PSCR further argued this was also consistent with the proposed refined Hurley Staging (Horvath et al 2017<sup>4</sup>), which proposed that selecting the population by requiring 5 ANs in at least 2 anatomical locations is the most appropriate basis for selecting candidates for treatment with biologic therapies. The PSCR also stated that trial design and recruitment criteria for biologics for moderate to severe HS have changed since the adalimumab trials, with other agents currently in clinical trials using similar disease criteria for recruitment as the secukinumab trials.
- 6.20 The ESC considered that while descriptions and measurement of moderate to severe HS in clinical trial design may be changing (compared to the older adalimumab trials), was also concerned this difference introduced additional uncertainty to the ITC, as patients in the secukinumab trials had more ANs at baseline and therefore more capacity for improvement, which may bias against adalimumab. The Pre-PBAC Response argued the key disease characteristics (Table 7 above) showed that except for the adalimumab M10-467 study, patients in the adalimumab trials had a slightly lower AN count and higher draining fistulae count compared to the secukinumab trials, and further argued the PIONEER and SHARPS populations had a greater proportion with Hurley Stage III disease, meaning the adalimumab trials overall likely had more severe disease. On that basis, the Response argued it was difficult to draw conclusions whether the patient characteristics of the secukinumab or adalimumab trials bias one way or the other based on individual characteristics of note.
- 6.21 The PSCR also argued the secukinumab studies recruited a population that included participants having previously failed a biologic therapy (which was not possible for adalimumab as a first in class biologic for HS), with ~86-92% of those having failed or

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<sup>4</sup> Horváth, B., Janse, I. C., Blok, J. L., Driessen, R. J., Boer, J., Mekkes, J. R., Prens, E. P., & van der Zee, H. H. (2017). Hurley Staging Refined: A Proposal by the Dutch Hidradenitis Suppurativa Expert Group. *Acta dermato-venereologica*, 97(3), 412–413. <https://doi.org/10.2340/00015555-2513>

not tolerated prior biologic therapies. The PSCR argued the inclusion of these patients biases the ITC in favour of adalimumab, as the secukinumab trial populations included a substantial proportion who had failed a prior biologic and therefore should be considered harder to treat.

- 6.22 The ESC noted the results of subgroup analysis for patients who have received prior biologics resulted in inconsistent directionality of ORs between SUNRISE (decrease from ITT, Q2W/Q4W OR = 1.75/1.48 to 1.27/1.28) and SUNSHINE (increase from ITT, Q2W/Q4W OR = 1.64/ 1.90 to 2.01/2.27). The ESC also noted there were numerous transitivity issues (discussed in the PSCR and paragraph 6.12) and considered, given the limited available data and lack of sizeable subgroups upon which to analyse potential impacts further, that it was not possible to draw clear conclusions about the directionality and magnitude of potential biases in the ITC.

**Table 8: Summary of results of the indirect comparison in HiSCR50 response**

	Proposed medicine n/N(%)	Comparator placebo n/N(%)	OR (95% CI)
<b>SEC vs PBO (SUNRISE &amp; SUNSHINE Wk16)</b>			
Q4W	158.3/360 (44.0)	117.8/363 (32.5) <sup>a</sup>	1.62 (1.20, 2.20)
Q2W	157.7/361 (43.7)	117.8/363 (32.5) <sup>a</sup>	1.62 (1.19, 2.19)
Q2W and Q4W Combined	316/721 (43.8)	117.8/363 (32.5) <sup>a</sup>	1.62 (1.24, 2.11)
<b>Adalimumab vs PBO (Wk12/16)<sup>b</sup></b>			
M10-467	24 / 44 (54.5%)	11 / 43 (25.6%)	3.49 (1.41, 8.64)
PIONEER I	64 / 153 (41.8%)	40 / 154 (26.0%)	2.05 (1.26, 3.32)
PIONEER II	96 / 163 (58.9%)	45 / 163 (27.6%)	3.76 (2.36, 5.98)
SHARPS	49 / 103 (47.6%)	35 / 103 (34.0%)	1.76 (1.01, 3.09)
Pooled analysis	233 / 463 (50.3%)	131 / 463 (28.3%)	2.56 (1.74, 3.77)
<b>Indirect comparisons</b>			
SEC (Q4W) vs adalimumab (pooled)			0.63 (0.39, 1.03)
SEC (Q2W) vs adalimumab (pooled)			0.63 (0.39, 1.04)
SEC (combined) vs adalimumab (pooled)			0.63 (0.40, 1.01)
SEC (combined) vs adalimumab (pooled, with SHARPS removed)			0.55 (0.33, 0.92)

Source: Table 2.62, p 128 of the submission. Additional analysis with removal of the SHARPS study performed in Review Manager 5.4.

CI= confidence interval; HiSCR50 = hidradenitis suppurativa clinical response of at least 50%; n=number of subjects with response; N= number of subjects evaluable; OR= odds ratio; PBO= placebo; Q2W= every 2 weeks; Q4W= every 4 weeks; SEC=secukinumab.

<sup>a</sup> Placebo Q2W and Q4W arms were pooled together for analyses.

<sup>b</sup> The primary efficacy outcomes of the adalimumab trials were measured at Week 16, apart from M10-467 which measured at Week 12.

**Bold** indicates a statistically significant result.

- 6.23 The ESC noted the SHARPS trial was in a different setting than for standard ongoing treatment of HS and considered its inclusion in the ITC was inappropriate. The ESC further noted that when the SHARPS trial was excluded from the ITC, the results indicated secukinumab was statistically significantly inferior to adalimumab in terms of HiSCR50 response rates. The Pre-PBAC Response acknowledged the SHARPS trial was in a different population than the other adalimumab or secukinumab trials, however also noted other inclusion criteria such as number of active regions, Hurley staging of disease and abscess count at baseline were similar to the other studies. Further, the Pre-PBAC Response noted the magnitude of response in SHARPS was lower than that observed in the PIONEER studies, but argued it was informative for a

population with more advanced disease and it was included in a recent systematic review and meta-analysis of trials of HS conducted in 2021<sup>5</sup>; and therefore, it was reasonable to include SHARPS in the ITC.

### ***Comparative harms***

6.24 The submission provided data on adverse events (AEs), serious AEs (SAEs), AEs resulting in discontinuation and deaths across the trials. Generally, AE rates were similar between intervention and placebo groups, and a placebo-anchored ITC comparing key safety outcomes between secukinumab and adalimumab did not suggest any clinically relevant differences in the safety profiles of the two treatments. SAEs and AEs resulting in discontinuations were low and generally balanced across the trials. Key safety data and a summary of the ITC are presented in Table 9 below. Treatments were well tolerated, with similar AEs compared to placebo arms. Across all trials, only two deaths were reported (both in the SHARPS trial) and considered to be unrelated to treatment. The safety data were generally consistent with the known safety profile of secukinumab in other conditions.

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<sup>5</sup> Lu, J. W., et al. (2021). "Efficacy and safety of adalimumab in hidradenitis suppurativa: A systematic review and meta-analysis of randomized controlled trials." *Medicine* 100:22: e26190.

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Table 9: Summary of results of key safety data in the key secukinumab trials, and an ITC with the adalimumab trials

	Proposed medicine n/N(%)	Comparator placebo n/N(%)	OR <sup>a</sup> (95% CI)
<b>SUNSHINE and SUNRISE (combined) SEC vs PBO (Wk16)</b>			
<b>Any AE</b>			
Q4W	232 / 360 (64.4%)	236 / 363 (65%)	0.97 (0.64,1.49)
Q2W	235 / 361 (65.1%)	236 / 363 (65%)	1.00 (0.74,1.36)
Q4W & Q2W	467 / 721 (64.8%)	236 / 363 (65%)	0.99 (0.76,1.29)
<b>Any SAE</b>			
Q4W	9 / 360 (2.5%)	11 / 363 (3%)	0.83 (0.33, 2.07)
Q2W	9 / 360 (2.5%)	11 / 363 (3%)	0.83 (0.33, 2.07)
Q4W & Q2W	18 / 721 (2.5%)	11 / 363 (3%)	0.82 (0.38, 1.75)
<b>Any AE resulting in discontinuation</b>			
Q4W	5 / 360 (1.39%)	5 / 363 (1.38%)	1.01 (0.29, 3.54)
Q2W	6 / 361 (1.66%)	5 / 363 (1.38%)	1.14 (0.06, 21.79)
Q4W & Q2W	11 / 721 (1.53%)	5 / 363 (1.38%)	1.11 (0.38, 3.22)
<b>Indirect comparisons</b>			
<b>Any AE</b>			
SEC (Q4W) vs adalimumab (pooled)			1.03 (0.65, 1.64)
SEC (Q2W) vs adalimumab (pooled)			1.06 (0.67, 1.69)
SEC (combined) vs adalimumab (pooled)			1.05 (0.68, 1.63)
<b>Any SAE</b>			
SEC (Q4W) vs adalimumab (pooled)			0.78 (0.34, 1.82)
SEC (Q2W) vs adalimumab (pooled)			0.81 (0.35, 1.88)
SEC (combined) vs adalimumab (pooled)			0.80 (0.35, 1.83)
<b>Any AE resulting in discontinuation</b>			
SEC (Q4W) vs adalimumab (pooled)			1.84 (0.33, 10.23)
SEC (Q2W) vs adalimumab (pooled)			1.37 (0.06, 29.63)
SEC (combined) vs adalimumab (pooled)			1.34 (0.34, 5.28)

Source: Extracted from Table 2.63, pp129-131 of the submission.

AE = adverse event; CI= confidence interval; n=number of subjects with response; N= number of subjects evaluable; NA= not applicable; OR= odds ratio; PBO= placebo; Q2W= every 2 weeks; Q4W= every 4 weeks; SAE= serious adverse event; SEC=secukinumab.

<sup>a</sup> Odds ratios >1 indicate more adverse events associated with secukinumab, and <1 indicate more adverse events associated with placebo or adalimumab.

Note: Results for other efficacy measures using relative risk and risk difference are provided in Attachment 10 of the submission. ORs for secukinumab trials in indirect comparisons were those calculated in Review Manager 5.4.

## Benefits/harms

6.25 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

## Clinical claim

6.26 The submission described secukinumab as superior compared to placebo in terms of effectiveness, and non-inferior to adalimumab. This claim was not adequately supported by the available evidence, which suggested secukinumab may provide a modest benefit over placebo in the SUNRISE/SUNSHINE trial populations, noting that this benefit is uncertain in the proposed PBS population, and the Q4W arm of SUNSHINE failed to demonstrate a statistically significant benefit over placebo. The ITC suggested that secukinumab may be inferior to adalimumab in terms of efficacy, as measured by the HiSCR50 response rate, particularly when the impact of removing

the SHARPS (adalimumab) study from the ITC is considered.

- 6.27 A range of applicability and transitivity issues were identified between the key secukinumab trials and target PBS population, as the existing restrictions were based on the on the adalimumab PIONEER and M10-467 trial populations (discussed in paragraph 6.12). Most of these differences likely favoured the apparent efficacy of secukinumab, adding uncertainty to the ITC results and whether the benefits described by the two key secukinumab trials would be realised in the target PBS population.
- 6.28 The ESC considered, given the results of the ITC to adalimumab excluding the SHARPS trial (paragraph 6.16 refers), combined with the transitivity and applicability issues identified and the inability to draw clear conclusions about potential biases, that secukinumab was likely to be of inferior comparative effectiveness to adalimumab for the treatment of moderate to severe HS.
- 6.29 The submission described secukinumab as inferior to placebo and non-inferior to adalimumab in terms of safety. The evaluation and ESC considered this claim was adequately supported.
- 6.30 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data, and the available evidence suggested secukinumab may be inferior to adalimumab.
- 6.31 The PBAC considered that the claim of non-inferior comparative safety for secukinumab and adalimumab was reasonable.

### ***Economic analysis***

- 6.32 The submission presented a CMA comparing secukinumab with adalimumab. The equi-effective doses were based on the recommended daily doses and estimated as secukinumab 300 mg on weeks 0, 1, 2, 3 and 4 and then at 4 weekly intervals and adalimumab 160 mg at day 1, followed by 80 mg at day 15, then 80 mg every 2 weeks (or 40 mg weekly) from day 29 over a 2-year time horizon (29 administrations of secukinumab and 53 administrations of adalimumab over 2 years). In forming this relativity, the submission assumed that secukinumab is at least as effective and safe as adalimumab, however non-inferiority of clinical outcomes was not clearly demonstrated by the submission.
- 6.33 The CMA was based on a Q4W maintenance dosing schedule of secukinumab. The submission presented a sensitivity analysis with the cost-minimised price of secukinumab based on Q2W dosing, however, did not consider a weighted approach. Based on maintenance dosing every two weeks the cost of secukinumab was reduced by 46.3% to \$607.44 per dose.
- 6.34 For the CMA the submission used an AEMP of \$818.54 for 1 dose of adalimumab 80 mg. In April 2023, adalimumab was subject to statutory price reductions with the published approved ex-manufacturer price (AEMP) reduced to \$618.90 per 80 mg

dose for the reference biologic (Humira) and the price of 4 biosimilars reduced to \$761.98 per 80 mg dose. Based on an adalimumab AEMP of \$618.90 per 80 mg dose the equivalent AEMP for secukinumab 300 mg/mL and 150 mg/mL was \$1,131.09. The results of the CMA are presented in Table 10.

**Table 10: Results of the cost-minimisation approach with the revised adalimumab AEMP (based on secukinumab maintenance dosing every 4 weeks)**

Component	Proposed medicine	Comparator
Cost per dose	\$1,131.09	\$618.90
Dose duration	2 years	2 years
Administrations over two years	29	53
Total medicine cost over two years	\$32,802	\$32,802

Source: Table 3.3, 140 of the submission and updated by the evaluation.  
Results of the CMA based on the revised AEMP of adalimumab (\$618.90; April 2023).

6.35 The ESC advised, given its view the claim of non-inferior comparative effectiveness to adalimumab was not adequately supported, that the cost minimisation approach proposed in the submission was inappropriate.

### **Secukinumab cost/patient/year**

6.36 The drug cost per patient for secukinumab and adalimumab is presented in Table 11. The cost per patient per year was based on the adalimumab price at time of submission (i.e. not accounting for the price reduction which took effect on 1 April 2023).

**Table 11: Drug cost per patient per year for proposed and comparator drugs**

	Secukinumab trial dose and duration	Secukinumab CMA	Secukinumab financial estimates	Adalimumab trial dose and duration	Adalimumab CMA	Adalimumab financial estimates
Mean dose/scripts	13.1 doses <sup>a</sup>	14.5 doses <sup>b</sup>	14.5 doses <sup>b</sup>	NR	26.5 doses <sup>c</sup>	26.5 doses <sup>c</sup>
DPMQ per script	\$1,209.00			\$675.94		
Cost/patient/year	\$15,838	\$17,531	\$17,531	NE	\$17,912	\$17,912

Source: constructed during evaluation

CMA= cost-minimisation approach; NE= not estimated; NR= not reported.

<sup>a</sup> Actual dose intensity in the trials (13.1 injections x 300 mg) (pooled data from SUNSHINE and SUNRISE).

<sup>b</sup> Averaged over 2-years treatment (16x300 mg doses in year 1 and 13x300 mg in year 2).

<sup>c</sup> Averaged over 2-years treatment (27x80 mg doses in year 1 and 26x80 mg in year 2).

### **Estimated PBS usage & financial implications**

6.37 This submission was not considered by DUSC.

6.38 The submission used a market share approach to estimate the extent of use and financial implications of listing secukinumab for the treatment of moderate to severe HS on the PBS. The market size of HS was approximated by using Medicare statistics to derive the number of adalimumab prescriptions for the treatment of HS following its inclusion on the PBS in July 2017. The submission assumed that a proportion of patients failing adalimumab would receive secukinumab as a second line therapy. The assumed use as second line therapy represents an expansion of the HS market. Uptake rate and proportion of use in second line treatment subsequent to adalimumab failure were assumed in the submission. The key inputs for the financial estimates are shown

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in Table 12.

**Table 12. Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Historic # of adalimumab scripts for HS	Yr 2017: 931 Yr 2018: 4,268 Yr 2019: 6,014 Yr 2020: 7,011 Yr 2021: 9,262 Yr 2022: 11,454  Mean annual growth of 2,105 scripts yearly used to project utilisation in subsequent years. Based on Medicare Statistics of adalimumab utilisation in HS.	Estimating annual growth based on the number of adalimumab scripts since listing may overestimate the rate of growth over the long term, as this was the first listing for HS and there was likely a prevalent pool of patients in this period.
Uptake rate	Yr 1: 10% Yr 2: 16% Yr 3: 22% Yr 4: 28% Yr 5: 34% Yr 6: 40% Assumption	The evaluation considered uptake in later years may be overestimated given the unclear clinical benefit of secukinumab presented in the submission.
Patients failing adalimumab	10% relative to secukinumab use yearly. Assumption	The submission assumed that 10% of secukinumab usage was attributable to patients who failed adalimumab and would receive secukinumab as a second line therapy. The use of secukinumab in second line after adalimumab failure was likely underestimated given the proportion of HS patients receiving adalimumab without an observed clinical response in real world evidence <sup>a</sup> (29.5%) and the lack of other pharmaceutical treatment options after adalimumab failure on the PBS.

Source: Table 4.2, p144, Table 4.3, p144, Table 4.6, p148 and Table 4.7, p150, of the submission.

HS= hidradenitis suppurative; PBS = Pharmaceutical Benefits Scheme.

<sup>a</sup> Gulliver, W., Alavi, A., Wiseman, M.C., Gooderham, M.J., Rao, J., Alam, M.S., Papp, K.A., Desjardins, O. and Jean, C. (2021), Real-world effectiveness of adalimumab in patients with moderate-to-severe hidradenitis suppurativa: the 1-year SOLACE study. *J Eur Acad Dermatol Venereol*, 35: 2431-2439. <https://doi.org/10.1111/jdv.17598>

6.39 The total net cost to the PBS/RPBS of listing secukinumab was estimated to be \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million in the first 6 years of listing, see Table 13.

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Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	1	1	1	2	2	3
<b>Estimated financial implications of secukinumab</b>						
Cost to PBS/RPBS less copayments	4	4	4	4	5	5
<b>Estimated financial implications for adalimumab</b>						
Cost to PBS/RPBS less copayments	6	6	6	6	6	6
<b>Net financial implications</b>						
Net cost to PBS/RPBS	4	4	4	4	4	4

Source: Table 4.7, p150. Of the submission.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

<sup>a</sup> Assuming 1:1 script equivalence with adalimumab as estimated by the submission.

on the revised DPMQ of secukinumab cost-minimised on the basis of the updated price of adalimumab (\$618.90; April 2023).

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$10 million to < \$20 million

<sup>6</sup> net cost saving

6.40 As a result of the additional usage of secukinumab among patients in the adalimumab failure subgroup, there was a net cost to the PBS/RPBS associated with the listing of secukinumab for HS. The utilisation and financial implications may have been underestimated for the following reasons (Table 14):

- The submission assumed that 10% of secukinumab usage was attributable to patients who failed adalimumab and would receive secukinumab as a second line therapy. The utilisation of secukinumab, attributed to patients who did not respond to adalimumab, should have been relative to patients receiving adalimumab, rather than being implemented as a fixed proportion of secukinumab usage. The submission did not provide sufficient evidence to support the proposed failure rate assumption (equivalent to an adalimumab failure rate of 1% in Year 1 to 7% of total scripts in Year 6). Real world evidence suggests that in approximately 30% of adalimumab patients a clinical response is not observed. Given the lack of further pharmaceutical treatment options available to HS patients the assumed rate of secukinumab after adalimumab failure may be underestimated. Based on the assumption that 20% of adalimumab scripts will require subsequent secukinumab due to failure of adalimumab the net cost to PBS/RPBS increased to \$0 to < \$10 million in Year 6.
- The submission assumed that all patients using secukinumab would receive Q4W maintenance dosing. This underestimated the net cost to the PBS/RPBS of the proposed listing. The submission has not identified what proportion of patients may benefit from the Q2W dosing schedule. While the proportion of patients that may utilise secukinumab Q2W in the maintenance phase remains unclear, assuming 10% of secukinumab usage is Q2W, the resulting net cost to the

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PBS/RPBS increases to \$0 to < \$10 million in Year 6.

- The proposed dosage in the draft PI is 300 mg administered subcutaneously with initial dosing at weeks 0, 1, 2, 3, and 4, which is equivalent to 5 vials over 5 weeks of treatment. However, the submission assumed that the initiation phase with secukinumab requires only 4 vials/syringes and included the 5<sup>th</sup> vial in the balance of supply period.

**Table 14: Key sensitivity analysis results for the proposed listing of secukinumab**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Base case</b>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
<b>Secukinumab usage subsequent to adalimumab failure (base case 10% relative to secukinumab use →20% of adalimumab use)</b>						
Net cost to PBS/RPBS	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
Change from baseline	700%	745%	712%	411%	283%	193%
<b>Revised script equivalence (base case 1:1 → 1:0.8 in initiation, 1.33:1 in BoS and 1:1 in maintenance)</b>						
Net cost to PBS/RPBS	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
Change from baseline	18%	10%	11%	18%	18%	18%
<b>Utilisation of secukinumab Q2W (maintenance) (base case 0% → 10%)</b>						
Net cost to PBS/RPBS	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
Change from baseline	34%	74%	114%	97%	97%	97%

Source: Produced during the evaluation using the updated adalimumab AEMP April 2023.

PBS = Pharmaceutical Benefits Scheme; Q2W = once every 2 weeks; RPBS = Repatriated Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

6.41 The utilisation and financial estimates are highly sensitive to the number of patients who use secukinumab as a second line therapy (i.e. subsequent to adalimumab), as all use in this line of therapy represents an incremental cost.

6.42 The ESC considered the assumption that only 10% of patients would likely escalate to a Q2W dose represented an underestimate and was of this view this was likely to be much higher in practice. The ESC considered the submission underestimated the proportion of patients who failed adalimumab and subsequently moved to secukinumab (equivalent to an adalimumab failure rate of 1% in Year 1 to 7% of total scripts in Year 6).

### **Financial Management – Risk Sharing Arrangements**

6.43 The submission expects that secukinumab will be required to enter the same Risk Sharing Arrangement (RSA) as adalimumab for HS. Additionally, the submission requested an increase in the current RSA cap to capture the additional use of secukinumab due to patients who are inadequately managed with adalimumab (adalimumab failure group). The submission stated the request is supported on the basis that under the proposed pricing, secukinumab would be at least as cost-effective as adalimumab (and more cost-effective for these patients who have no other viable treatment options).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the General Schedule, Authority Required listing of secukinumab (SEC) for the treatment of moderate to severe hidradenitis suppurativa (HS). The Committee considered there was a high clinical need for additional therapies for the treatment of HS. The PBAC considered SEC provides a modest benefit compared to placebo but the claim that SEC was non-inferior to adalimumab (ADA) in terms of effectiveness was uncertain. The PBAC considered the extent of uncertainty regarding the effectiveness claim may be acceptable in the context of the high clinical need if there was additional certainty regarding the cost minimised price for SEC and the net PBS/RPBS cost.
- 7.2 The primary reason for this outcome was due to the economic evaluation.
- 7.3 The PBAC considered there was a high need for additional pharmacological treatment options for HS, as ADA was currently the only therapy subsidised for moderate to severe HS after other options such as antibiotics have been found to be ineffective or not tolerated. The Committee noted there was strong consumer support for additional treatment options for HS, and further noted the comments from patients and clinicians described the historical underdiagnosis of HS in practice, and the severe burden of disease and impacts on quality of life people with HS experienced (discussed further in 'Consumer comments'). The PBAC also noted the comments described that for some patients, the effectiveness of current treatments had waned over time, with painful and repeated surgical procedures among the limited options available.
- 7.4 The Committee noted that patients in the SEC trials had response to therapy measured later than what currently occurs with the ADA PBS listing (after 16 weeks versus 12-16 weeks for the ADA listing) and that patients were not required to have trialled and not responded to prior antibiotics to be eligible for the SEC trials (the current ADA PBS listing requires two prior courses). However, the PBAC noted that more than 80% of the SEC trial population had previously received systemic antibiotics in the period since diagnosis (paragraph 6.14 refers) and agreed with the ESC that the SEC trials were likely to be broadly generalisable to the PBS population. On that basis, the PBAC considered it was reasonable that a future listing of SEC for HS should be under the same conditions as the current listings for ADA, however it may be reasonable to allow response to SEC to be assessed at 16-20 weeks (rather than 12-16 weeks) with appropriate quantities and repeats for initial treatment.
- 7.5 The PBAC considered the nominated comparator of ADA was reasonable.
- 7.6 The PBAC noted the submission was supported by two randomised controlled trials comparing SEC to placebo (SUNSHINE and SUNRISE), and the indirect comparison (ITC) was informed by four ADA trials (M10-467, PIONEER I/II and SHARPS). The Committee noted the primary outcome for most trials (except M10-467) was a HS clinical response of at least 50% (HiSCR50), and study M10-467 collected HiSCR50 outcome

data. The PBAC noted potential exchangeability issues across the SEC and ADA trials (paragraphs 6.7, 6.13-6.14 and 6.17 refer), in particular with the SHARPS trial which was undertaken in a perioperative setting.

- 7.7 The PBAC noted the HiSCR50 response rates for the two-weekly (Q2W) and four-weekly (Q4W) dosing regimens of SEC were statistically significantly higher than placebo, except for the Q4W arm of SUNSHINE. The PBAC also noted the SEC HiSCR50 response rates were below 50% at 16 weeks across both trials, and the response rates for the Q2W and Q4W regimens appeared to differ across the SUNSHINE and SUNRISE trials, with the Q2W regimen having a higher response rate in SUNSHINE and the Q4W regimen having a higher response rate in SUNRISE. Overall, the PBAC considered the available evidence indicated SEC was likely superior to placebo for the treatment of HS, but its effectiveness appeared to be relatively modest.
- 7.8 The PBAC noted the HiSCR50 response rates for SEC in SUNSHINE and SUNRISE were 42-46% (versus 31-34% for placebo) and for ADA in M10-467, PIONEER I and PIONEER II were 42-59% (versus 26-28% for placebo). The PBAC noted the ITCs potentially suggested that the effectiveness of SEC was inferior to that of ADA, however also acknowledged exchangeability issues across the trials and the higher placebo response rates in the SEC trials. Overall, the PBAC considered the claim that SEC was non-inferior to ADA in terms of effectiveness was uncertain.
- 7.9 The PBAC noted the key safety data and ITCs did not suggest clinically important differences in comparative safety between SEC and ADA, and that the safety data for SEC in HS were consistent with the known safety profile of SEC. Overall, the PBAC considered the claim of non-inferior comparative safety of SEC and ADA to be reasonable.
- 7.10 The PBAC considered treatment with SEC was likely to be more costly than treatment with ADA as the submission did not account for any use of the Q2W maintenance dosing schedule or response being measured at a later timepoint than for ADA.
- 7.11 The PBAC noted the submission estimated there was a net cost to the PBS/RPBS associated with the listing of SEC for HS due to additional usage in the ADA failure subgroup. The PBAC considered the utilisation and financial estimates to be underestimated due to underestimating the extent of use in patients who have failed ADA and not including utilisation of the Q2W maintenance dose of secukinumab.
- 7.12 The PBAC considered the extent of uncertainty regarding the effectiveness claim may be acceptable in the context of the high clinical need if there was additional certainty regarding the cost minimised price for SEC and the net PBS/RPBS cost. In this context, the PBAC considered the outstanding issues could be easily resolved in a simple resubmission for SEC using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.
- Present a revised CMA which addresses the issues raised in paragraph 7.10; and

- Present revised financial estimates which account for use of the Q2W regimen and more reliably estimate the extent of use in patients who have failed treatment with ADA.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Novartis is pleased to see the PBAC recognised there was a high clinical need for additional therapies for the treatment of HS and will continue to work with the PBAC to enable earliest possible access to secukinumab for HS patients.