



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Secukinumab

Proprietary Product Name: Cosentyx

Sponsor: Novartis Pharmaceuticals Australia Pty  
Ltd

**January 2021**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
Anti-TNF-IR	Inadequate/intolerant anti-tumour necrosis factor responder
ARTG	Australian Register of Therapeutic Goods
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20	Assessment of SpondyloArthritis International Society 20% response
ASAS40	Assessment of SpondyloArthritis International Society 40% response
ASAS 5/6	Assessment of SpondyloArthritis International Society 5/6 response
ASAS PR	Assessment of SpondyloArthritis International Society partial remission score
ASQoL	Ankylosing Spondylitis Quality of Life
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI 50	Bath Ankylosing Spondylitis Disease Activity Index $\geq$ 50% improvement
BASFI	Bath Ankylosing Spondylitis Functional Index
CI	Confidence interval
C <sub>min</sub>	Minimum concentration
CHMP	Committee for Medicinal Products for Human Use (European Union)
CRP	C-reactive protein
CSR	Clinical study report
DMARD	Disease modifying anti-rheumatic drug
EU	European Union

Abbreviation	Meaning
FDA	Food and Drug Administration (United States)
hsCRP	High sensitivity C-reactive protein
IgG1	Immunoglobulin G1
IL-17	Interleukin 17
IV	Intravenous
MRI	Magnetic resonance imaging
nr-axSpA	Nonradiographic axial spondyloarthritis
NRI	Non-responder imputation
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
OSI	Objective signs of inflammation
PI	Product Information
PT	Preferred Term
PY	Patient years
Q4W	Every 4 weeks
r-axSpA	Radiographic axial spondyloarthritis
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form 36
SI	Sacroiliac
SOC	System Organ Class
SPARCC	Spondyloarthritis Research Consortium of Canada
TRAE	Treatment related adverse event
TNF $\alpha$	Tumour necrosis factor alpha

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Abbreviation	Meaning
TNFi	Tumour necrosis factor inhibitor
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
USA	United States of America
VAS	Visual analog scale

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Product name:</i>	Cosentyx
<i>Active ingredient:</i>	Secukinumab
<i>Decision:</i>	Approved
<i>Date of decision:</i>	10 September 2020
<i>Date of entry onto ARTG:</i>	17 September 2020
<i>ARTG numbers:</i>	AUST R 218798, 218799, 218800
<i>, Black Triangle Scheme:<sup>1</sup></i>	No
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road Macquarie Park NSW 2113
<i>Dose forms:</i>	Powder for injection; solution for injection (prefilled syringe); solution for injection (prefilled pen)
<i>Strengths:</i>	150 mg powder/vial; 150 mg/1 mL prefilled syringe; 150 mg solution prefilled pen
<i>Containers:</i>	Vial; prefilled syringe; prefilled pen
<i>Pack size(s):</i>	Prefilled pen: Packs of 1, and 2 pens Prefilled syringe: Packs of 1, and 1 syringes Powder for injection vial: Packs of 1, and 2 x 6 mL vials
<i>Approved therapeutic use:</i>	<i>Non-radiographic axial spondyloarthritis (axSpA without radiographic damage)</i>  <i>Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to, or are intolerant to, NSAIDs.</i>
<i>Route of administration:</i>	Subcutaneous injection

<sup>1</sup> The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

**Dosage:****Non-radiographic axial spondyloarthritis**

*With a loading dose:* The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month.

*Without a loading dose:* The recommended dose is 150 mg by subcutaneous injection every month.

*Assessment prior to initiation of Cosentyx:* Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with Cosentyx (see section 4.4. Special Warnings And Precautions For Use of the Product Information (PI)).

**Pregnancy category:**

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Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

**Product background**

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Cosentyx (secukinumab) 150 mg powder for injection (vial) and 150 mg solution for injection (prefilled syringe and prefilled pen) for the following proposed extension of indications:

*Nonradiographic axial spondyloarthritis (nr-axSpA), as part of axial spondyloarthritis (axSpA) with or without radiographic damage.*

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition predominantly manifested by back pain and progressive spinal stiffness that incorporates two subtypes, ankylosing spondylitis (AS, also described as radiographic axial spondyloarthritis, or r-axSpA) and non-radiographic axial SpA (nr-axSpA). Patients with AS and nr-axSpA report similar disease burden and symptoms. AS and nr-axSpA differ in that significant abnormalities of affected sacroiliac (SI) joints are observed by conventional radiography in patients with AS but not in those with nr-axSpA. In this population, the diagnosis is supported by evidence of active inflammation of the SI joints on magnetic resonance imaging (MRI) and other evidence of inflammation, for example elevated serum inflammatory markers. Approximately 5 to 10% of patients with nr-axSpA progress to AS within two years and approximately 20% within about five years.<sup>2</sup> While ankylosing spondylitis and nr-axSpA are often considered together, there remains uncertainty around

<sup>2</sup> Yu DT, van Tubergen A. Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. UpToDate. Last updated January 2020, accessed 22 June 2020



whether they represent distinct but overlapping disorders, or just different subgroups along a single axial SpA spectrum differing by severity or chronology of the illness.

This submission requests an extension of the registered treatment indications in Australia for secukinumab, which are currently restricted to plaque psoriasis, psoriatic arthritis and AS, to include the treatment of adults with active nr-axSpA.

Up until 2015, the TGA only approved biologic therapies for the limited axial SpA indication of clearly defined AS, owing to concerns about the broader axial SpA treatment indication and the need for a clearer delineation of nr-axSpA as a defined subset. The United States (US) Food and Drug Administration (FDA) took a similar position to the TGA. However, in recent years, following the publication of additional scientific data regarding nr-axSpA (natural history, definition and documentation of the objective signs of inflammation (OSI) associated with the entity), the TGA has approved a small number of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibiting (anti-TNF) therapies for the treatment of nr-axSpA. Current treatment options in Australia for nr-axSpA therefore include nonsteroidal anti-inflammatory drugs (NSAID) and the following anti-TNF drugs:

*Golimumab: Non-radiographic axial spondyloarthritis (nr-Axial SpA)*

*Simponi is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).*

*Etanercept: Non-radiographic axial spondyloarthritis*

*Treatment of adults with active\* non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.*

*\*Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of  $\geq 4$ .<sup>3</sup>*

*Certolizumab pegol: Non-radiographic axial spondyloarthritis*

*Cimzia is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C reactive protein (CRP) and /or magnetic resonance imaging (MRI) change, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).*

Secukinumab is the first in class anti-interleukin (IL)-17 therapy proposed for registration in Australia to treat active nr-axSpA.

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The **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)** is a validated diagnostic tool and is considered to be a gold standard for measuring and evaluating ankylosing spondylitis disease activity. The BASDAI is typically conducted by a rheumatologist or allied healthcare professional and can assess the effectiveness of current drug therapy or interventions and/or the need for additional or alternative interventions.

The BASDAI consists of a 0 to 10 scale measuring discomfort, pain, and fatigue (0 being no problem and 10 being the worst problem) in response to six questions asked of the patient pertaining to the five major symptoms of ankylosing spondylitis: fatigue; spinal pain; arthralgia (joint pain) or swelling; enthesitis, or inflammation of tendons and ligaments (areas of localised tenderness where connective tissues insert into bone); morning stiffness duration; and morning stiffness severity. To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. Scores of 4 or more suggest suboptimal control of disease, and those patients are usually good candidates for a change in their medical therapy, may benefit by treatment with biologic therapies, or may be candidates for enrolment in clinical trials evaluating new drug therapies directed at treating the disease process.

## Regulatory status

### Australian regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in January 2015, approved for the treatment of plaque psoriasis, and subsequently the indication was extended to include psoriatic arthritis and ankylosing spondylitis (axial spondyloarthritis with radiographic damage) in May 2016.

More recently (2020), an application was approved to alter dosage for the ankylosing spondylitis (axial spondyloarthritis with radiographic damage) indication to permit a 300 mg maintenance dose based on clinical response, as opposed to 150 mg.

### Overseas regulatory status

In the United States of America (USA) secukinumab was approved for marketing by the United States (US) Food and Drug Administration (FDA) in June 2020 for the indication:

*Active non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients with objective signs of inflammation."*

Both loading and non-loading dose regimens were approved in the US, with subsequent doses every four weeks.

In the European Union (EU) secukinumab received a positive opinion from the EU Committee for Medicinal Products for Human Use (CHMP) in March 2020 for the following indication:

*For the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).*

The recommended dosage included loading doses at Weeks 0, 1, 2, 3 and 4, followed by monthly doses thereafter.

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 1: Timeline for Submission PM-2019-04601-1-3**

Description	Date
Submission dossier accepted and first round evaluation commenced	4 December 2019
First round evaluation completed	26 March 2020

Description	Date
Sponsor provides responses on questions raised in first round evaluation	28 May 2020
Second round evaluation completed	16 June 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 July 2020
Sponsor's pre-Advisory Committee response	17 July 2020
Advisory Committee meeting	6/7 August 2020
Registration decision (Outcome)	10 September 2020
Completion of administrative activities and registration on the ARTG	17 September 2020
Number of working days from submission dossier acceptance to registration decision*	146 days

\*Statutory timeframe for standard applications is 255 working days

### III. Submission overview and risk/benefit assessment

#### Quality

There was no requirement for a quality evaluation in a submission of this type.

#### Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

#### Clinical

The clinical dossier included one Phase III efficacy and safety study (Study CAIN457H2315 (also known as the PREVENT trial) further referenced in this document as Study H2315), and a pooled safety data set where safety data from Study H2315 was pooled with safety data from nine other clinical studies in ankylosing spondylitis (AS), psoriatic arthritis and plaque psoriasis.

#### Pharmacology

##### *Pharmacokinetics*

The pharmacokinetic characteristics of secukinumab in patients with nr-axSpA are similar to the previously characterised pharmacokinetics of secukinumab in adult patients with AS. Secukinumab exhibits moderate variability in serum trough concentrations in adult subjects with axSpA. At Week 4, secukinumab trough concentrations (mean  $\pm$  standard deviation (SD)) in subjects who received a loading regimen of 150 mg SC secukinumab at Weeks 0, 1, 2 and 3 ( $53.1 \pm 16.0 \mu\text{g/mL}$ ) were 5-fold those measured in the no load group

who had only received 150 mg secukinumab at Week 0 ( $10.5 \pm 4.3 \mu\text{g/mL}$ ). Both secukinumab treatment groups received 150 mg secukinumab at Week 4 and each 4 weeks after. By Week 16, the mean trough concentration in the loaded group was  $28.5 \pm 11.0 \mu\text{g/mL}$  and in the unloaded group was  $20.6 \pm 8.0 \mu\text{g/mL}$ . By Week 52, the steady state mean serum concentrations of secukinumab were 22.8 and 22.4  $\mu\text{g/mL}$  in the loaded treatment arm ( $n = 98$  subjects) and the no load arm ( $n = 106$  subjects), respectively.

One patient showed treatment-emergent ADA at Week 52 only in the Phase III Study H2315.

#### ***Population pharmacokinetic data***

None submitted.

#### ***Pharmacodynamics***

No new data submitted.

#### **Efficacy**

##### ***Study CAIN457H2315 (PREVENT trial)***

This study is an ongoing, randomised, double blind, parallel group, placebo controlled Phase III trial in 555 adults primarily designed to demonstrate the efficacy of secukinumab 150 mg therapy (with or without a loading dose regimen) versus placebo on the signs and symptoms of active nr-axSpA. The trial consists of a core phase (up to Week 104) and an extension phase (Weeks 104 to 208), although the data presented in the dossier were only available from study reports at Week 24 and after Week 52. The secukinumab dose regimens chosen for evaluation in the study were based on doses used in two pivotal Phase III trials in adult subjects with active AS. Two separate analysis plans were developed for this study, to satisfy different requirements for regulators in the USA (primary efficacy analysis at Week 52), and for regulators in the EU and other non-USA regions (primary efficacy analysis at Week 16). The original submission included a clinical study report summarising all efficacy results up to Week 24, and efficacy results for patients who had completed their week 52 visit by the cut-off date of 17 December 2018. Results presented here are from the EU analysis plan, unless otherwise stated.

Patients were screened up to 10 weeks prior to Baseline to determine eligibility for the trial and to provide for wash-out of any prohibited medications. At Baseline, eligible patients were randomised at a ratio of 1:1:1 to one of three treatment groups: secukinumab 150 mg at 0, 1, 2, 3 and 4 weeks, then 4-weekly thereafter (loaded regimen), secukinumab 150 mg at 0 weeks and then 4-weekly thereafter (no load regimen), or matched placebo SC injections. Based on the clinical judgement of disease activity by the investigator, background medications such as NSAIDs and disease-modifying anti-rheumatic drugs (DMARD) could be modified or added to treat signs and symptoms of nr-axSpA, but only from Week 16 onwards. Furthermore, patients who were deemed to be inadequate responders at two or more consecutive visits, based on the clinical judgement of the investigator, could receive secukinumab 150 mg SC therapy or other biologics as standard of care treatment from Week 20 onwards. Starting at Week 52, all patients were assigned to receive secukinumab 150 mg therapy in an open-label manner except for those patients who had discontinued blinded study treatment (secukinumab or placebo) during the initial 52 weeks of the trial.

Inclusion and exclusion criteria reflect the common criteria in clinical trials for this population. Key criteria for participants were that they must have had a documented diagnosis of adult onset axSpA according to Assessment in Spondyloarthritis International Society (ASAS) criteria, objective signs at screening of SI joint inflammation on centrally-read MRI and/or a high sensitivity (hs) C-reactive protein (CRP) value > upper limit of normal (ULN) on central screening. Patients were ineligible if sacroiliitis was evident on

plain X-rays as defined by the modified New York (mNY) criteria.<sup>4</sup> Active disease at Baseline was determined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score  $\geq 4$ ;<sup>3</sup> spinal pain  $\geq 4$  by visual analogue scale (VAS) and total back pain  $> 40$  mm by VAS.<sup>5</sup> Participants must also have had an inadequate response to, had a contraindication to, or been intolerant to at least two NSAIDs. Prior exposure to one anti-TNF $\alpha$  therapy was allowed if the drug had been discontinued for at least three months prior to randomisation following inadequate response or intolerance (anti-TNF-IR). While the initial protocol allowed for a maximum of 30% of the population to be anti-TNF-IR, this estimate was revised by protocol variation to a maximum of 20%. However, in the final population only 9.7% of participants had received a prior anti-TNF medication. Randomisation was centrally conducted and stratified according to the patient subgroup by objective signs of inflammation (OSI). The OSI classification criteria produced three subgroups:

- CRP+/MRI+ (29.9%);
- CRP-/MRI+ (42.3%); or
- CRP+/MRI- (27.7%).

The primary efficacy outcome was the Assessment of SpondyloArthritis International Society 40% response (ASAS40) rate at Week 16 in anti-TNF naïve subjects. An ASAS40 response is defined as a  $> 40\%$  improvement and an absolute improvement from Baseline of  $> 2$  units (range: 0 to 10) in at least three of four domains: back pain (10 cm VAS), patient global assessment of disease activity (10 cm VAS), physical function (assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI): range 0 to 10) and inflammation (mean score of items 5 and 6 of the BASDAI; both 10 cm VAS), without any worsening in the remaining domain. An ASAS40 response is considered to be of significant clinical benefit.

Pre-specified secondary efficacy outcomes were evaluated by anti-TNF status (naïve versus anti-TNF-IR) and OSI stratification. Comparisons of loaded secukinumab treatment versus placebo treatment were prioritised over comparisons of no loading secukinumab treatment versus placebo treatment.

The secondary outcomes in sequential testing order included:

- Proportion of subjects achieving ASAS 5/6 response at Week 16;<sup>6</sup>
- Mean change from Baseline in total BASDAI score at Week 16,
- Percentage of subjects achieving BASDAI 50 response at Week 16;<sup>7</sup>
- Mean change from Baseline in hsCRP at Week 16,

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<sup>4</sup> The **modified New York (mNY) criteria** (1984) for ankylosing spondylitis includes the clinical criteria of low back pain  $\geq 3$  months, improved by exercise and not relieved by rest; limitation of lumbar spine in sagittal and frontal planes; and limitation of chest expansion (relative to normal values corrected for age and sex); plus the radiological criteria of bilateral grade 2-4 sacroiliitis, or; unilateral 3-4 sacroiliitis.

<sup>5</sup> A **Visual Analogue Scale (VAS)** is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. The pain VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases.

<sup>6</sup> The **Assessment of SpondyloArthritis International Society 5/6 response (ASAS 5/6)** improvement criteria include six domains: patient global, pain, function (assessed by BASFI), inflammation (mean of BASDAI questions 5 and 6), CRP, and spinal mobility (assessed by lateral spinal flexion). In order to meet an ASAS 5/6 improvement, there should be an improvement of at least 20 % in at least five of these six domains.

<sup>7</sup> The **Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI 50)** is defined by improvement of at least 50 % in the BASDAI score or an absolute change of 2 units (on a 0 to 10 scale) after 3 months of treatment, together with an expert opinion compatible with improvement.

- Mean change from Baseline in BASFI at Week 16;<sup>8</sup>
- Mean change from Baseline in SI joint SPARCC score at Week 16;<sup>9</sup>
- Proportion of subjects reaching ASAS20 response at Week 16;<sup>10</sup>
- Mean change from Baseline in SF-36 PCS at Week 16;<sup>11</sup>
- Mean change from Baseline in the ASQoL at Week 16;<sup>12</sup> and
- Proportion of subjects achieving ASAS partial remission at Week 16.

MRI scans of the spine and SI joints were performed at Baseline, Week 16 (+/- 2 weeks) and Week 52.

The analysis of the primary efficacy endpoint was based on a logistic regression model fitted with treatment group (secukinumab loaded, secukinumab no loading, placebo) and OSI classification as factors, and with weight as a covariate. Odds ratios (OR) with associated 95% confidence intervals (CI) were computed using the logistic regression model for comparisons of efficacy outcomes between secukinumab versus placebo. Participants who discontinued their randomised study treatment for any reason prior to Week 16 were considered non-responders (non-responder imputation, NRI). Similarly, subjects who did not have sufficient available data to compute the ASAS response at baseline or any time thereafter were also classified as non-responders. Sensitivity testing using observed data, multiple imputation and a tipping point analysis were performed to test the integrity of the primary analysis.

Using the hierarchical analysis strategy, the primary and all secondary efficacy endpoints were met at 16 weeks. The ASAS40 response rate at 16 weeks in anti-TNF naïve patients in the secukinumab loaded group (68/164, 41.5%) was statistically significantly higher than in the placebo group (50/171, 29.2%,  $p = 0.0197$ , Hypothesis 1). Similarly, the ASAS40 response rate in the secukinumab no load arm (70/166, 42.2%) was statistically higher than with placebo treatment ( $p = 0.0146$ , Hypothesis 13) as shown in Table 2, below.

<sup>8</sup> The **Bath Ankylosing Spondylitis Functional Index (BASFI)** includes 10 questions; 8 of them refer to aspects of functional anatomy, and 2 pertain to the ability to cope with everyday life. All questions are completed on numerical rating scales or on a 10 cm visual analogue scale (VAS) with 'easy' and 'impossible' as polar opposites. The total BASFI-score is the average of the 10 questions and ranges from 0 to 10.

<sup>9</sup> The **Spondyloarthritis Research Consortium of Canada (SPARCC)** methodology is designed as a magnetic resonance imaging index for scoring inflammation in the spine.

<sup>10</sup> The **Assessment of SpondyloArthritis International Society 20 response (ASAS20)** is defined as a > 20% improvement and an absolute improvement from Baseline of >2 units (range: 0 to 10) in at least three of four domains: back pain (10 cm VAS), patient global assessment of disease activity (10 cm VAS), physical function (Bath Ankylosing Spondylitis Functional Index (BASFI): range 0 to 10) and inflammation (mean score of items 5 and 6 of the BASDAI; both 10 cm VAS), without any worsening in the remaining domain.

<sup>11</sup> The **Short Form 36 (SF-36)** is a standardised, self-reported measure of functional health and well-being. The SF-36 was designed to be a brief yet comprehensive measure of general health status. The SF-36 questionnaire consists of eight scales yielding two summary measures: physical and mental health.

<sup>12</sup> The **Ankylosing Spondylitis Quality of Life (ASQoL)** is a quality of life instrument specific to ankylosing spondylitis.

**Table 2: Study H2315 (PREVENT trial) ASAS40 response rates at Week 16 for anti-TNF naïve participants (non-responder imputation)**

Analysis Visit	Treatment Group	n/M(%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=164)	68/164 (41.5)	vs. No Load	0.98	(0.63, 1.51)	0.9165
			vs. Placebo	1.72	(1.09, 2.70)	0.0197
	AIN457 150 mg No Load (N=166) Placebo (N=171)	70/166 (42.2) 50/171 (29.2)	vs. Placebo	1.76	(1.12, 2.76)	0.0146

CI= confidence interval

Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and baseline weight as a covariate.

Missing responses for any reason were imputed as non-responders.

n: The number of patients who responded.

M: The total number of patients in the treatment group of the specified analysis set.

Higher response rates in secukinumab treated groups were sustained at Week 52 (secukinumab load 47/133, 35.3%; secukinumab no load 47/132, 35.6%; placebo 25/132, 18.9%; interim analysis).

The ASAS40 response rates at 16 weeks in anti-TNF naïve patients were numerically higher in CRP+/MRI+ participants (secukinumab loaded 26/49, 53.1%; no load 28/52, 53.8%) than in CRP+/MRI- participants (loaded 16/45, 35.6%; no load 15/44, 34.1%) and CRP-/MRI+ (loaded 26/70, 37.1%; no load 27/70, 38.6%). While the study was not powered to examine statistical differences in response rates in subgroups, it is noted that in the CRP+/MRI+ participants response rates in the both secukinumab treated arms were higher than in the placebo arm, this difference was not seen in the CRP+/MRI- or CRP-/MRI+ groups (placebo response rates: CRP+/MRI+ 22.0%; CRP+/MRI- 33.3%; CRP-/MRI+ 31.6%). This finding suggests that the overall difference in the primary efficacy outcome may be driven by the response rates in the CRP+/MRI+ subgroup.

**Table 3: Study H2315 (PREVENT trial) Efficacy results (full analysis set, hierarchical testing strategy)**

Hypothesis	Endpoint	Comparison vs. Placebo	Unadjusted p-value	Adjusted p-value Testing hierarchy	Statistically Significant
H1	ASAS40 in TNF-alpha naïve patients at Week 16	AIN457 150 mg Load	0.0197	0.0197	Yes
H2	ASAS40 at Week 16	AIN457 150 mg Load	0.0108	0.0197	Yes
H3	ASAS 5/6 at Week 16	AIN457 150 mg Load	0.0005	0.0197	Yes
H4	BASDAI at Week 16	AIN457 150 mg Load	0.0006	0.0197	Yes
H5	BASDAI50 at Week 16	AIN457 150 mg Load	0.0001	0.0197	Yes
H6	hsCRP at Week 16	AIN457 150 mg Load	0.0002	0.0197	Yes
H7	BASFI at Week 16	AIN457 150 mg Load	0.0041	0.0197	Yes
H8	SI joint edema on MRI at Week 16	AIN457 150 mg Load	<.0001	0.0197	Yes
H9	ASAS20 at Week 16	AIN457 150 mg Load	0.0260	0.0260	Yes
H10	SF-36 PCS at Week 16	AIN457 150 mg Load	0.0006	0.0260	Yes
H11	ASQoL at Week 16	AIN457 150 mg Load	0.0008	0.0260	Yes
H12	ASAS partial remission criteria at Week 16	AIN457 150 mg Load	<.0001	0.0260	Yes
H13	ASAS40 in TNF-naïve patients at Week 16	AIN457 150 mg No Load	0.0146	0.0260	Yes

**Table 4: Study H2315 (PREVENT trial) Efficacy results (full analysis set, hierarchical testing strategy) (continued)**

H14	ASAS40 at Week 16	AIN457 150 mg No Load	0.0087	0.0260	Yes
H15	ASAS 5/6 at Week 16	AIN457 150 mg No Load	0.0094	0.0260	Yes
H16	BASDAI at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H17	BASDAI50 at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H18	hsCRP at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H19	BASFI at Week 16	AIN457 150 mg No Load	0.0143	0.0260	Yes
H20	SI joint edema on MRI at Week 16	AIN457 150 mg No Load	<.0001	0.0260	Yes
H21	ASAS20 at Week 16	AIN457 150 mg No Load	0.0149	0.0260	Yes
H22	SF-36 PCS at Week 16	AIN457 150 mg No Load	0.0011	0.0260	Yes
H23	ASQoL at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H24	ASAS partial remission criteria at Week 16	AIN457 150 mg No Load	0.0001	0.0260	Yes

In the full analysis set ASAS40 response rates at Week 16 in the secukinumab loaded arm (74/184, 40.0%) and in the secukinumab no load arm (75/184, 40.8%) were both significantly higher than in the placebo arm (52/186, 28.0%;  $p = 0.011$ ,  $p = 0.009$ , respectively). This was reflected in the CRP+/MRI+ subgroup where response rates in secukinumab treated arms (loaded 29/54, 53.7%; no load 29/57, 50.9%) were numerically greater than in the placebo arm (12/55, 21.8%), but not in the CRP+/MRI- (loaded 18/52, 34.6%, no load 16/51, 31.4%, placebo 15/51, 29.4%) or in the CRP-/MRI+ (loaded 27/79, 34.2%, no load 30/76, 39.5%, placebo 25/80, 31.3%). ASAS40 response rates to placebo in the CRP+/MRI- and CRP-/MRI+ groups were numerically somewhat higher than seen in the CRP+/MRI+ subgroup.

ASAS40 response rates at Week 16 in secukinumab treated groups were numerically higher in anti-TNF naïve subjects compared with anti-TNF-IR patients (secukinumab loaded 6/21, 28.6%; secukinumab no load 5/18, 27.8%; placebo 2/15, 13.3%). Response rates to placebo were lower than seen in other subgroups. Small group size (< 10% of the full population) is a likely contributor to this variability.

In the full analysis set, ASAS5/6 response rates at Week 16 in CRP+/MRI+ participants in the secukinumab treated arms (> 50%) were also numerically higher than in placebo arm (20.0%). This difference was not reflected in the CRP+/MRI- participants (loaded 36.5%, no load 35.3%, placebo 33.3%). In the CRP-/MRI+ participants, the ASAS5/6 response rate in the loaded arm was 34.2%, in the no load arm was 23.7% and in the placebo arm was 20.0%. The ASAS5/6 response rates in the anti-TNF-IR subgroup were similar in secukinumab treated arms and placebo treated participants.

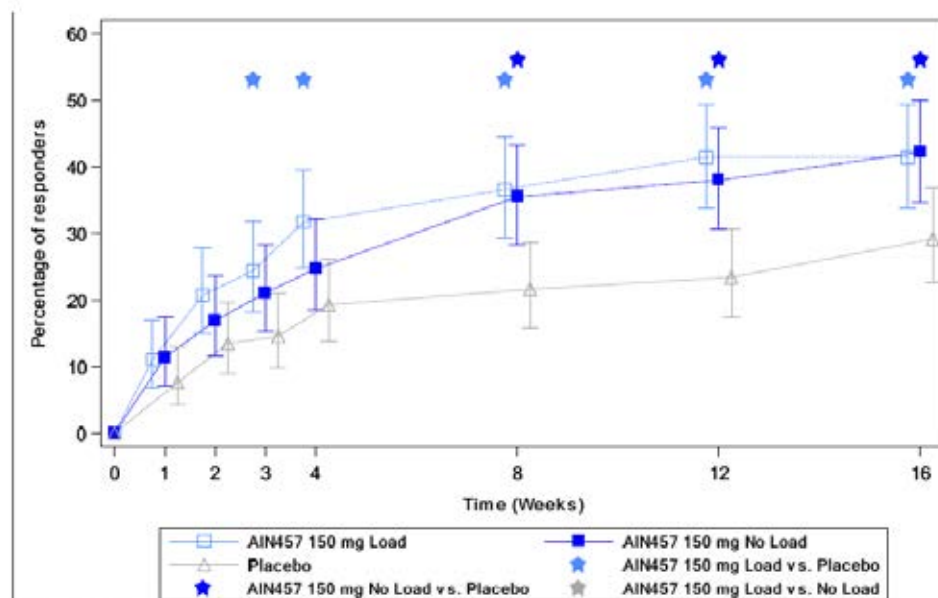
Overall, the secondary outcomes BASDAI change from Baseline, BASDAI50, BASFI change from Baseline, ASAS20, SF-36 PCS and MCS changes from Baseline, AsQoL and ASAS partial remission in the full analysis population at 16 weeks were significantly better in the secukinumab treatment arms than in the placebo arm. Again, the results appeared to be predominantly driven by the anti-TNF naïve and CRP+/MRI+ groups, with no numerical differences in the response rates between secukinumab treated arms and placebo arm in most analyses for CRP+/MRI-, CRP-/MRI+ and anti-TNF-IR subgroups. MRI improvements at 16 weeks (SI joint oedema mean change from baseline) in the full analysis set were significantly greater in the secukinumab treated arms than in placebo arm, this was also reflected numerically in the CRP-/MRI+ group as well as in the CRP+/MRI+ group, although not in CRP+/MRI- or anti-TNF-IR groups.

Using a time response curve analysis (Weeks 1, 2, 3, 4, 8, 12 and 16) with unadjusted p-values of 0.05 as the cut-off for statistical significance, higher ASAS40 response rates were observed with secukinumab versus placebo in TNF-naïve patients from Week 3 onwards for the secukinumab 150 mg load group, and from Week 8 onwards for the



secukinumab 150 mg no load arm. Although ASAS40 response rates in the secukinumab loaded group were numerically higher than in the no loading secukinumab group, that difference was not statistically significant at any time point (see following figure).

**Figure 1: Study H2315 (PREVENT trial) ASAS40 response over time (as a percentage, with 95% confidence intervals) in TNF-alpha naïve patients (non-responder imputation)**



\* Unadjusted p-value  $\leq 0.05$

Source: Table 14.2-1.1

An interim analysis of Week 52 data (US FDA analysis) included 71.5% of study participants with data available at database lock. The study met the primary efficacy endpoint for ASAS40 response rates in TNF-naïve patients at Week 52. For anti-TNF naïve patients, the rate of ASAS40 response at Week 52 was higher in both secukinumab treatment groups (44/114, 38.6% with loading; and 44/115, 38.3% with no secukinumab load) compared to 20.2% (24/119) in the placebo arm.

## Safety

Cumulative exposure to secukinumab in Study H2315 at the data cut-off date was 228.3 patient years (PY) for the secukinumab load group and 234.6 PY for the no load secukinumab arm. Including patients who switched from placebo at any time between 24 weeks and 52 weeks, cumulative exposure to secukinumab overall was 588.0 PY. The median duration of exposure to secukinumab was 419.0 days for the secukinumab loaded group, 451.0 days for the secukinumab no load group and 394.5 days for any secukinumab treatment.

Treatment related adverse events (TRAE) were reported at a higher incidence in the secukinumab groups compared to placebo for the entire treatment period: 40.5% (75/185) in the loaded secukinumab group and 29.3% (54/184) in the no load secukinumab arm versus 18.3% (34/186) in the placebo group. The major contributor to this imbalance between the groups during the entire study period was mainly in the System Order Class (SOC) of 'Infection' (29.7% in the loaded secukinumab group and 17.4% in the no load secukinumab arm versus 11.3% in the placebo group) predominantly due to differences in the incidence of nasopharyngitis followed by upper respiratory tract infections (URTI) and urinary tract infections by Preferred Term (PT) across the three groups.

Other SOCs where differences were reported in the three arms included Gastrointestinal Disorders: 5.9%(11/185) in the loaded secukinumab group and 7.6% (14/184) in the no load secukinumab arm versus 3.2% (6/186) in the placebo group mainly due to a higher frequency of nausea adverse events (AE) by PT in the two secukinumab groups and diarrhoea AEs in the no load secukinumab arm; and General Disorders and Administration Site Conditions.

No deaths were reported for the entire treatment period of Study H2315. However, non-fatal serious adverse events (SAE) occurred more frequently in the loaded secukinumab treatment group compared to the two other arms: 8.1% (15/185) with loaded secukinumab therapy versus 4.3% (8/184) with no load secukinumab treatment and 3.8% (7/186) with placebo. Up to Week 20, the frequency of SAEs was similar between the three treatment cohorts.

The safety data up to Week 16 in Study H2315 was compared with safety data in other treatment indications to evaluate the need to update the current list of AEs during placebo controlled treatment periods. Data from four trials in psoriasis (Studies A2302, A2303, S2308 and A2309, all 12 weeks), two in psoriatic arthritis (Studies F2306 and F2312, both 16 weeks) and two in AS (Studies F2305 and F2310, both 16 weeks) were pooled with data from Study H2315. A side-by-side comparison of the frequencies of treatment-emergent AEs between Studies H2315 and F2310 (in patients with AS, up to Week 16) was also provided in the submission. In both studies, the primary analysis was performed at Week 16 before placebo group subjects were allowed the option to switch to open-label secukinumab. Overall, the safety profile for secukinumab in nr-axSpA patients in Study H2315 is comparable to that of secukinumab treatment in AS patients in Study F2310, based upon the overall frequency of AEs in the two studies and the similarities in the most commonly occurring AEs per SOC. Incidence rates in the loaded secukinumab 150 mg group and the no load secukinumab arm of Study H2315 were comparable to those treated with loaded secukinumab therapy in Study F2310. AEs in the placebo group of Study F2310 were slightly more frequent than reported in Study H2315.

### **Clinical evaluator's opinion**

The clinical evaluator has recommended approval (as follows below) however recommends a secukinumab regimen without loading over the sponsor's preferred dosage regimen:

The clinical evaluator recommends acceptance of the sponsor's proposed extension of treatment indication for secukinumab to include the treatment of patients with active nr-axial SpA. The current submission provides robust evidence of improving the symptoms and signs of active nr-axial SpA, as well as physical functioning and health related outcomes. The improvements are obtained at an acceptable safety risk and patients with nr-axial SpA do not show any significant variations (increased incidence or change in pattern of AEs) from the known safety profile of secukinumab.

However, the clinical evaluator recommends the proposed wording of the nr-axial SpA treatment indication be more specific in defining the objective signs of inflammation and specify that it is a second line treatment after a trial of NSAID. A more detailed treatment indication wording would be consistent with supporting trial dataset as well as the approved treatment indication wording for anti-TNF drugs in this population.

The proposed indication is:

*Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by*

*elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to, or are intolerant to, NSAIDs.*

In this submission, the sponsor has additionally evaluated the effect of using a loading dose regimen at initiation of secukinumab treatment versus treatment without loading. Analysis Plan A of Study H2315 demonstrated that both regimens of secukinumab were equally efficacious at 16 weeks of treatment follow-up and the sponsor is justifying the registration of the loading regimen based on earlier time responses (in weeks) for a chronic condition. The posology at initiation of secukinumab treatment is an outstanding contentious issue for which the sponsor needs to provide clinical reasoning. Study H2315 is a well conducted Phase III trial in a well-defined disease population with nr-axial SpA (as per the internationally recognised and valid 2009 ASAS Classification Criteria). Furthermore, patients were assessed and analysed according to validated objective signs of inflammation criteria (elevated CRP and/or MRI changes). Patients with active nr-axial SpA demonstrated treatment responses to secukinumab that are of a similar magnitude of benefit to that seen in patients with active AS, and there no significant differences in the safety profile of the drug across the axial SpA treatment subsets.

## Risk management plan

No evaluation was required for this submission.<sup>13</sup> The absence of a risk management plan (RMP) for the new indication was acceptable to the TGA. No additional safety concerns or changes in the safety profile were identified during the evaluation. The most recent RMP was submitted in November 2019.

## Risk-benefit analysis

### Delegate's considerations

#### *Proposed indication*

The sponsor requested an extension of indication for secukinumab for the treatment of patients with active nr-axSpA. The submission was supported by one ongoing Phase III efficacy and safety trial in 555 participants. Based on the inclusion and exclusion criteria described in the protocol the extension of indication includes clear descriptors of the proposed population, that is:

#### ***Non-radiographic axial spondyloarthritis (axSpA without radiographic damage)***

*Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to, or are intolerant to, NSAIDs.*

The amended indication is somewhat supported by the data provided in the submission, and aligns with indications for other biological medicines (TNF $\alpha$  inhibitors) approved for the treatment of nr-axSpA in Australia. Approval of the proposed indication also aligns with approvals in international jurisdictions.

The evaluator noted that the overall ASAS40 response rate to placebo in anti-TNF naïve patients was somewhat higher than had been reported in the literature assessing other

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<sup>13</sup> The sponsor must still comply with routine product vigilance and risk minimisation requirements.

treatment options for nr-axSpA. In response to a TGA request for further information, the sponsor suggested that the high placebo response may reflect the subjective nature of the major efficacy outcome measures, which are made up of composite endpoints. The sponsor referred to lower response rates to 'higher hurdle' secondary endpoints in placebo treated patients to support this opinion. Nevertheless, there appears to be significant variability in placebo response rates in different OSI sub-groups that merits further consideration. The sponsor has been asked to address this issue in a pre-ACM response.

The sub-group analysis identifies that the response rates to secukinumab appear to be driven by better responses at 16 weeks in the CRP+/MRI+ population, which do not statistically appear to extend to CRP+/MRI- or CRP-/MRI+ subgroups. These two subgroups, making up some 70% of the participants in the trial, represent a significant proportion of the population of axSpA that may not respond to secukinumab as well as the group data suggest.

A similar concern may be raised with regard to extension of the indication to anti-TNF-IR patients. This population was not well represented in the study and accurate analysis of response rates is limited by small numbers. Nevertheless, with response rates to secukinumab considerably lower than seen in anti-TNF naïve populations, and potentially matching response rates to placebo, there may be a case for not routinely offering secukinumab for the treatment of axSpA in anti-TNF-IR patients.<sup>14</sup> There are currently no head to head comparisons of the efficacy of secukinumab and the TNF $\alpha$  inhibitors to assess whether secukinumab should be trialled before these drugs.

In view of the variability in efficacy among different subgroups of the nr-axSpA population, this delegate recommends that patients who have failed to respond to, or who are intolerant to treatment with NSAIDs, who satisfy the other criteria for nr-axSpA, may consider a trial of secukinumab, which should be ceased if there is no evidence of a reasonable clinical response by 16 weeks of treatment.

### ***Proposed dose regimen***

The sponsor requests approval of a dosing regimen of:

*...150mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4 followed by the same dose every month.*

The sponsor has provided sufficient evidence that subcutaneous injections of secukinumab every four weeks, with or without initial loading doses of 150 mg at 1, 2 and 3 weeks, provide significantly greater improvements in the signs and symptoms of nr-axSpA over placebo at sixteen weeks (at least in some subgroups of the nr-axSpA population), and that the benefit over placebo in responders is sustained at least until 52 weeks. Although actual dosing during the studies occurred every four weeks rather than monthly, this difference is unlikely to have a significant effect on efficacy or safety in the longer term. The study is still ongoing and further long-term efficacy and safety data can be provided.

The sponsor has shown that improvements in the primary efficacy outcome (ASAS40 at 16 weeks in the TNF naïve population) in secukinumab loaded patients are statistically significantly better than in placebo treated patients from three weeks of treatment. While at the same time points, ASAS40 responses in secukinumab loaded and secukinumab no load regimens are not statistically significantly different (see Figure 1, above), neither is the response rate in the secukinumab no load regimen statistically significantly different from response rate in the placebo group. The sponsor argues that the secukinumab no

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<sup>14</sup> Sponsor clarification: Refer to the sponsor's response to the Delegate's Questions for sponsor (specifically Question 2) on Page 23 for further clarification on response rates in TNF-IR patients.

load regimen only shows statistical improvements over placebo at eight weeks of treatment, which is a clinically important delay that may be avoided by applying the loading dose. As the evaluator has identified, adverse events reports are more frequent in the first 20 weeks of treatment and overall with the secukinumab loaded regimen, although absolute event rates between the loaded and no loaded regimen are numerically not grossly different. Adverse event reports are comparable to those reported in the AS population, who carry a similar burden of disease as the nr-axSpA group.

This Delegate recommends that the choice between a loaded or no loading regimen for secukinumab be left to the decision of the patient and treating physician, with due consideration of patient factors that may contribute to increased experience of adverse reactions, previous experience with other medications and the likelihood of a significant clinical response.

### ***Deficiencies of the data***

While the sponsor had intended that up to 30% of the trial population could comprise of patients who had an inadequate response or intolerance of TNF $\alpha$  inhibitors, some 10% of the final analysis set were from this subgroup. Logistic regression analyses of the secondary efficacy outcomes were stratified by anti-TNF status. Numerically, efficacy responses in this population were somewhat lower than in anti-TNF naïve population, which has been reported with other biological medicines. The low enrolment of this population subgroup has contributed to some uncertainty regarding the likely effectiveness of secukinumab, particularly in view of broad variability in the response rates to placebo. In the absence of conclusive data regarding efficacy in this subset, but also acknowledging that patients who have not responded to NSAIDs or TNF $\alpha$  inhibitors have no other treatment options, it is this delegate's opinion that a trial of secukinumab may be appropriate, with cessation at 16 weeks in the absence of clinical response.

### **Proposed regulatory action**

Pending advice from the Advisory Committee on Medicines (ACM) and the sponsor's pre-ACM response, the Delegate considers the benefit/risk profile of secukinumab to be positive and recommends approval for the indication:

#### ***Non-radiographic axial spondyloarthritis (axSpA without radiographic damage)***

*Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to, or are intolerant to, NSAIDs*

Pending advice from the ACM, the Delegate recommends that both dosing regimens be approved for use, that is to say:

***Without a loading dose:*** *The recommended dose is 150 mg by subcutaneous injection every four weeks.*

***With a loading dose:*** *The recommended dose is 150 mg by subcutaneous injection every four weeks with initial dosing at Weeks 0, 1, 2, 3, and 4.*

*Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment.*

### ***Outstanding issues***

Pending advice from the ACM and pre-ACM response from the sponsor, some aspects of the Product Information are yet to be confirmed.

### **Conditions of registration**

The sponsor must submit the final clinical study reports of the fully completed pivotal Study CAIN457H2315 (or Study H2315 as referenced earlier in this document), including, but not restricted to, results addressing the maintenance of response after treatment of withdrawal and results of immunogenicity studies, on completion of the study.

### **Request for Advisory Committee advice**

1. What is the view of the Committee on the relative benefits and risks of the loading regimen compared to the unloaded regimen?

What is the view of the Committee on the clinical importance of the numerically higher response rate (as measured by ASAS40 in anti-TNF naïve patients) in the first eight weeks in the secukinumab loaded arm compared to secukinumab no load arm?

2. What is the view of the Committee on the evidence supporting efficacy of secukinumab in anti-TNF-IR populations?
3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### **Questions for sponsor**

1. With reference to the primary efficacy outcome in anti-TNF naïve study participants at 16 weeks, please comment on why the ASAS40 response rate to placebo in CRP+/MRI+ participants (22%) was apparently lower than the response rate to placebo in CRP+/MRI- (33.3%) and CRP-/MRI+ (31.6%) participants? The evaluator queried the overall response rate to placebo in the anti-TNF naïve population (29.2%) compared to other published studies.
2. Noting that the response rates to secukinumab (loaded and no load arms) at 16 weeks for the primary and secondary outcomes in the anti-TNF-IR participants were generally not different to response rates in the placebo arm, please justify including anti-TNF-IR patients in the indication.

### **Sponsor's response to delegate's questions**

1. ***With reference to the primary efficacy outcome in anti-TNF naïve study participants at 16 weeks, please comment on why the ASAS40 response rate to placebo in CRP+/MRI+ participants (22%) was apparently lower than the response rate to placebo in CRP+/MRI- (33.3%) and CRP-/MRI+ (31.6%) participants? The evaluator queried the overall response rate to placebo in the anti-TNF naïve population (29.2%) compared to other published studies.***

Akin to the influence of objective signs of inflammation based on magnetic resonance imaging (MRI) and/or C-reactive protein (CRP) positivity at Baseline on efficacy with TNF inhibitors (TNFi), as seen the example of golimumab, Study H2315 showed the highest efficacy with the lowest placebo responses in the subgroups which were CRP+ and/or MRI+ across efficacy outcomes in patients with nr-axSpA. Both elevation of CRP and evidence of inflammation in the sacroiliac joints (SI joints) on MRI are well established objective assessments for disease activity in patients with nr-axSpA.

Therefore, higher placebo response rates in patients with lesser objective signs of inflammation such as might be seen in the subgroups of patients with CRP+/MRI- and CRP-/MRI+ may be expected and reflected in the ASAS40 response rates. Notably for high hurdle efficacy outcomes such as ASAS partial remission placebo response rates for the

CRP+/MRI- (7.8%) and CRP-/MRI+ (7.5%) patients were comparable to the placebo response rates in CRP+/MRI+ (5.5%) patients.

**2. Noting that the response rates to secukinumab (loaded and no load arms) at 16 weeks for the primary and secondary outcomes in the anti-TNF-IR participants were generally not different to response rates in the placebo arm, please justify including anti-TNF-IR patients in the indication.**

The robustness of the data supporting the efficacy of secukinumab in both TNFi-naïve and TNF-IR nr-axSpA patients is confirmed by the comparison of efficacy responses based on non-responder imputation at Week 16 of TNF-IR patients against those of TNFi-naïve patients. It is well known that TNF-IR patients have lower absolute response rates both for the active biologic and for placebo than TNF-naïve patients, thus it is important to look at treatment differences versus placebo in order to make comparisons. As outlined in the following table, there are no meaningful differences between the two subgroups in terms of calculated treatment differences against placebo. This confirms the similar efficacy of secukinumab in both subgroups. The robustness of the evidence of efficacy in TNF-IR patients is further supported by the consistent results of benefit across key efficacy endpoints.

**Table 5: Study H2315 TNFi-naïve versus TNF-IR efficacy responses based on non-responder imputation at Week 16 (full analysis set)**

	TNFi-naïve			TNF-IR		
	AIN457 150 mg Load	Placebo	Calculated difference between the rates of AIN457 150 mg Load and placebo <sup>1</sup>	AIN457 150 mg Load	Placebo	Calculated difference between the rates of AIN457 150 mg Load and placebo <sup>1</sup>
ASAS40, n/M (%)	68/164 (41.5)	50/171 (29.2)	12.3%	6/21 (28.6)	2/15 (13.3)	15.3%
ASAS 5/6, n/M (%)	68/164 (41.5)	43/171 (25.1)	16.4%	6/21 (28.6)	1/15 (6.7)	21.9%
BASDAI50, n/M (%)	64/164 (39.0)	38/171 (22.2)	16.8%	5/21 (23.8)	1/15 (6.7)	17.1%
ASAS20, n/M (%)	97/164 (59.1)	81/171 (47.4)	11.7%	8/21 (38.1)	4/15 (26.7)	11.4%
ASAS partial remission, n/M (%)	37/164 (22.6)	13/171 (7.6)	15%	3/21 (14.3)	0/15 (0.0)	14.3%

n: number of patients who responded; M: total number of patients in the treatment group of the specified analysis set

<sup>1</sup> Percentages are based on observed data of the primary estimand with using non responder imputation for treatment switch and missing data. Source: [CAIN457H2315 W24 CSR-Table 14.2-2.3b], [CAIN457H2315 W24 CSR-Table 14.2-3.3b], [CAIN457H2315 W24 CSR-Table 14.2-5.3b], [CAIN457H2315 W24 CSR-Table 14.2-9.3b], [CAIN457H2315 W24 CSR-Table 14.2-13.3b]

In addition, secukinumab has already demonstrated clear efficacy across multiple autoimmune indications in TNF-IR patients, including psoriasis, psoriatic arthritis, and AS). In particular, IL-17A blockade is the only other cytokine-based biologic other than TNF-inhibition shown to effectively treat AS, which falls along the same disease spectrum as nr-axSpA sharing similar clinical features, disease severity, and response to treatment (Wallis 2013).

### Advisory Committee considerations<sup>15</sup>

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

<sup>15</sup> The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory

### ***Specific advice to the delegate***

The ACM advised the following in response to the Delegate's specific request for advice:

**1. *What is the view of the Committee on the relative benefits and risks of the loading regimen compared to the unloaded regimen?***

***What is the view of the Committee on the clinical importance of the numerically higher response rate (as measured by ASAS40 in anti-TNF naïve patients) in the first eight weeks in the secukinumab-loaded arm compared to the non-loading arm?***

In assessing the relative benefits and risks of the loading regime, the ACM determined that there was utility in a loading dose. Clinical studies have demonstrated a response lag in unloaded patients. Although the difference in response between loaded and unloaded patients disappears by Week 16 of treatment, the difference at earlier stages (Weeks 3 to 4) is clinically important enough for the ACM to conclude that the loading regime offers advantages for some patients. Although the loading regime has been associated with a higher incidence of adverse events, particularly infections, these are mild in nature and outweighed by improvements in patient response. The ACM was of the view that decisions regarding whether to pursue a loaded regimen or an unloaded regimen is best made clinically by the treating rheumatologist.

**2. *What is the view of the Committee on the evidence supporting the efficacy of secukinumab in anti-TNF-IR populations?***

The ACM noted that the studies under consideration were not adequately powered to investigate the effects of secukinumab on TNF-experienced patients; with lower responses reported to both treatment and placebo. Though the numbers were too low to be of statistical significance, the ACM concluded that it is possible that secukinumab may be of benefit in TNF experienced patients and this group should not be excluded from consideration given the lack of alternative treatment options.

**3. *The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application***

The committee had no other advice to provide to the Delegate regarding this application.

### ***Conclusion***

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

*Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or MRI change, who have had an inadequate response to, or are intolerant to, NSAIDs.*

### **Outcome**

Based on a review of quality, safety and efficacy, the TGA approved the registration of:

- Cosentyx secukinumab (rch) 150 mg powder for injection vial
- Cosentyx secukinumab (rch) 150 mg/1 mL solution for injection in prefilled syringe
- Cosentyx secukinumab (rch) 150 mg/1 mL solution for injection in prefilled pen

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Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.



Indicated for the following extension of indications:

***Non-radiographic axial spondyloarthritis (axSpA without radiographic damage)***

*Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to, or are intolerant to NSAIDs.*

The full indications are now:

***Plaque psoriasis***

*Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.*

***Psoriatic arthritis***

*Cosentyx is indicated for the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.*

***Axial spondyloarthritis (axSpA) with or without radiographic damage***

***Ankylosing spondylitis (axSpA with radiographic damage)***

*Cosentyx is indicated for the treatment of adult patients with active ankylosing spondylitis.*

***Non-radiographic axial spondyloarthritis (axSpA without radiographic damage)***

*Cosentyx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to, or are intolerant to, NSAIDs.*

**Specific conditions of registration applying to these goods**

This approval does not impose any requirement for the submission of Periodic Safety Update reports. You should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

You are reminded that sections 29A and 29AA of the Therapeutic Goods Act 1989 provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

- information that contradicts information already given by the person under this Act;
- information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
- information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;
- information that indicates that the quality, safety or efficacy of the goods is unacceptable.

## Attachment 1. Product Information

The PI for Cosentyx approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Therapeutic Goods Administration**

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