



Australian Government

Department of Health

Therapeutic Goods Administration

# Australian Public Assessment Report for Certolizumab pegol (rbe)

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

**February 2020**

## 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.
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- 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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## Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS40	Assessment of SpondyloArthritis International Society 40% response
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score - Major Improvement
ASQoL	Ankylosing Spondylitis Quality of Life
Axial SpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
CI	Confidence interval
CRP	C-reactive protein
DMARD	Disease-modifying anti-rheumatic drug
HIV	Human immunodeficiency virus
ISR	Injection site reaction
mNY	Modified New York (diagnostic criteria)
MRI	Magnetic resonance imaging
Nr-axial SpA	Non-radiographic axial spondyloarthritis
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds Ratio

Abbreviation	Meaning
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SI	Sacroiliac
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	Tuberculosis
TNF	Tumour necrosis factor
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
VAS	Visual Analogue Scale

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	13 November 2019
<i>Date of entry onto ARTG:</i>	18 November 2019
<i>ARTG numbers:</i>	154726, 281317
<b>▼</b> <i>Black Triangle Scheme</i>	No
<i>Active ingredient:</i>	Certolizumab pegol (rbe)
<i>Product name:</i>	Cimzia
<i>Sponsor's name and address:</i>	UCB Australia Pty Ltd Level 1, 1155 Malvern Road Malvern VIC 3144
<i>Dose form:</i>	Solution for injection
<i>Strength:</i>	200 mg/mL
<i>Container:</i>	Prefilled syringe or prefilled pen
<i>Pack size:</i>	2
<i>Approved therapeutic use:</i>	<i>Non-radiographic Axial Spondyloarthritis</i>  <i>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).</i>
<i>Route of administration:</i>	Subcutaneous
<i>Dosage:</i>	Cimzia treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis and plaque psoriasis. After proper training in injection technique, patients may self inject with Cimzia if their physician determines that it is appropriate and with medical follow-up as necessary.  <i>Loading dose</i>  The recommended loading dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each)

initially (Week 0) and at Weeks 2 and 4.

#### *Maintenance dose*

#### Non-radiographic Axial Spondyloarthritis

After the loading dose, the recommended dose of Cimzia for adult patients with non-radiographic axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.

For further information refer to the Product Information.

## Product background

This AusPAR describes the application by UCB Australia Pty Ltd (the sponsor) to extend the indications of Cimzia (certolizumab pegol (rbe)) solution for injection for the following proposed indication:

*[...] the treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.*

Axial spondyloarthritis (axial SpA) is a chronic inflammatory disease of the axial skeleton characterised by inflammation of the sacroiliac (SI) joints and spine. Patients with axial SpA report persistent back pain and spinal stiffness, as well as a reduction in mobility and quality of life. Axial SpA encompasses both ankylosing spondylitis and non-radiographic axial spondyloarthritis (nr-axial SpA). Patients with nr-axial SpA have little to no changes in the SI joints on plain radiographs and thus do not meet modified New York (mNY) criteria for a diagnosis of ankylosing spondylitis. Magnetic resonance imaging (MRI) enables the visualisation of active SI joint and spinal inflammation that is not evident with conventional X-rays. While ankylosing spondylitis and nr-axial SpA are often considered together, there remains uncertainty around 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. Patients with ankylosing spondylitis and nr-axial SpA report similar disease burden and symptoms.

Current treatment options in Australia for nr-axial SpA include nonsteroidal anti-inflammatory drugs (NSAIDs) and the two approved anti-tumour necrosis factor (TNF) drugs (golimumab and etanercept).

Certolizumab pegol (Cimzia) is a recombinant, humanised monoclonal antibody fragment that is conjugated to polyethylene glycol which binds with high specificity to TNF alpha. At the time the submission described in this AusPAR was under consideration, Cimzia was approved in specific adult populations with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis. The submission is supported by a pivotal Phase III clinical trial along with supportive data from a previous Phase III clinical trial and other studies.

This is a re-submission from the sponsor to extend the indications for Cimzia to include the treatment of adult patients with nr-axial SpA. The previous submission is discussed in the AusPAR for submission PM-2013-00286-2-3.

## Regulatory status

Cimzia (certolizumab pegol (rbe)) solution for injection in a prefilled syringe received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 January 2010 for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis on 20 January 2010 and a 200 mg/mL prefilled syringe was registered on 10 February 2017.

At the time the TGA considered this application, a similar application for the nr-axial SpA indication had been approved in the European Union (EU; 2013), Switzerland (2014) and United States of America (USA), and was under consideration in Canada (see Table 1).

**Table 1: International regulatory status of Cimzia (certolizumab pegol (rbe)), nonradiographic axial spondyloarthritis indication**

Region	Submission date	Status	Indications
EU (centralised procedure)	May 2013	Approved October 2013	<p><i>Axial spondyloarthritis</i></p> <p><i>Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:</i></p> <p><i>Ankylosing spondylitis (AS) (also known as radiographic axial spondyloarthritis)</i></p> <p><i>Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).</i></p> <p><i>Axial spondyloarthritis without radiographic evidence of AS (also known as non-radiographic axial spondyloarthritis)</i></p> <p><i>Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs</i></p>
Switzerland	April 2013	Approved November 2014	Nonradiographic Axial Spondyloarthritis was approved as a subset of the Ankylosing Spondylitis indication
USA	September 2018	Approved March 2019	<p><i>Non-radiographic Axial Spondyloarthritis</i></p> <p><i>Cimzia is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation [see Clinical Studies (14.5)].</i></p>
Canada	November 2018	Under consideration	Under consideration

## 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 2: Timeline for Submission PM-2018-04256-1-3**

Description	Date
Submission dossier accepted and first round evaluation commenced	31 December 2018
First round evaluation completed	31 May 2019
Sponsor provides responses on questions raised in first round evaluation	1 July 2019
Second round evaluation completed	30 July 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 August 2019
Sponsor's pre-Advisory Committee response	10 September 2019
Advisory Committee meeting	4 October 2019
Registration decision (Outcome)	13 November 2019
Completion of administrative activities and registration on ARTG	18 November 2019
Number of working days from submission dossier acceptance to registration decision*	193

\*Statutory timeframe for standard applications is 255 working days

## III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

### Quality

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

### Nonclinical

No nonclinical data specific to the extension of indications was submitted, but several updated pharmacokinetic (PK) analytical validation studies were submitted as further regulatory information. The nonclinical evaluator has advised there are no changes to any previous nonclinical conclusions arising from the present data.

## Clinical

The clinical dossier includes two Phase III studies:

- Study AS0006; a new pivotal 52 week study in nr-axial SpA which is ongoing; and
- Study AS001; a previously submitted study in axial SpA (that is, both nr-axial SpA and ankylosing spondylitis).

Integrated safety datasets of subjects with axial SpA in 4 clinical studies were also provided.

## Pharmacology

The pharmacokinetic (PK) characteristics of certolizumab in adult patients with ankylosing spondylitis and patients with nr-axial SpA have similar PK responses to certolizumab exposure. In Study AS0006, steady state drug concentrations were reached by Week 12 following multiple subcutaneous (SC) doses of 200 mg every two weeks (Q2W) and remained relatively stable through to Week 52. Both studies showed that trough serum concentrations were lower in those with high anti-drug antibody (ADA) titres (Study AS0006) or in those who developed treatment emergent ADAs (Study AS001). In Study AS001, positive ADA status was associated with a reduced rate of clinical efficacy response compared to ADA negative status. In Study AS0006, a *post-hoc* analysis showed no discernible relationship between the achievement of the clinical efficacy outcomes and ADA titre.

The two main sources of PK variability identified in certolizumab treated patients are subject body weight and the presence of ADA. The dossier did not include a population PK analysis to examine this effect. In the pivotal study, between Weeks 24 and 52, the geometric mean plasma certolizumab levels in heavier subjects were approximately 30 to 50% lower than lighter weighted subjects, however there is a lack of data on clinical response.

## Efficacy

### Study AS0006

The single pivotal Phase III study, Study AS0006, included in this submission examined the effect of one dose regimen compared to placebo, which was chosen based on the 24 week data from the preceding Study AS001. In that trial, 2 dose regimens were evaluated in an axial SpA population (same loading dose but maintenance doses of 200 mg Q2W or 400mg every 4 weeks (Q4W)) which demonstrated that both dose regimens were similarly efficacious.

Study AS0006 is an ongoing, randomised, double blind, multicentre, multinational, parallel group, placebo controlled Phase III trial that was primarily designed to demonstrate the efficacy of certolizumab pegol 200 mg Q2W in prefilled syringe (after a loading dose of 400 mg at Weeks 0, 2 and 4) versus placebo on the signs and symptoms in 317 adult subjects with active nr-axial SpA over 52 weeks. The interim study report was provided and the open label period is ongoing (Weeks 52 to 156). The study included a protocol amendment that involved changing the primary efficacy endpoint from an Ankylosing Spondylitis Disease Activity Score - Major Improvement (ASDAS-MI) response at Week 52;<sup>1</sup> to an Assessment of SpondyloArthritis International Society 40% response (ASAS 40)

<sup>1</sup> The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in ankylosing spondylitis. 3 cut-offs separate the degree of disease intensity: < 1.3 between 'inactive disease' and 'low disease activity', < 2.1 between 'moderate disease activity' and 'high disease activity', and > 3.5 between 'high disease activity' and 'very high disease activity'. A change  $\geq 1.1$  units defines a 'clinically important improvement' and a change  $\geq 2.0$  units for 'major improvement'.

at Week 12.<sup>2</sup> Patients in the study had adult onset axial SpA according to ASAS criteria (not including family history and good response to NSAIDs) and must not have had evidence of sacroiliitis on plain X-rays (bilateral grade > 2 or unilateral grade > 3; based on central reading of X-rays) as defined by the mNY criteria. Subjects were required to have experienced back pain for at least 12 months prior to screening. Patients also had active disease and a combination of current evidence for sacroiliitis on screening MRI and C-reactive protein (CRP) reading to produce 3 stratified groups: MRI+/CRP+, MRI+/CRP- or MRI-/CRP+. Patients must have had an inadequate response to, had a contraindication to, or been intolerant to at least 2 NSAIDs. The exclusion criteria (n = 30) were comprehensive and similar to other Phase III studies in axial SpA. Subjects with known tuberculosis (TB) exposure (present or past) were excluded, but those with latent TB could be included after treatment according to local country guidelines.

The primary efficacy endpoint was ASAS 40 response at Week 12, defined as a  $\geq 40\%$  improvement and an absolute improvement from Baseline of  $\geq 2$  units (range: 0 to 10) in at least 3 of the following 4 domains: back pain (10 cm Visual Analogue Scale (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 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); both 10 cm VAS) without any worsening in the remaining domain. An ASAS 40 response is considered to be of significant clinical benefit. Key endpoints used validated metrics and secondary endpoints were adjusted for multiplicity. Study completion was 78.6% for certolizumab and 34.1% for placebo. There were no clinically significant differences between the two treatment groups at Baseline with respect to demographic characteristics and both were also reasonably well balanced with respect to baseline disease features. The baseline characteristics were representative for patients with active nr-axial SpA and the disease activity scores at baseline are consistent with moderate to severe axial SpA activity. At least 20% of the randomised subjects, as designed, belonged to each of the 3 clinical subgroups stratified by objective signs of inflammation (MRI and CRP) at Baseline.

The primary efficacy outcome of ASAS 40 response rate at Week 12 was significantly higher in the certolizumab versus placebo groups (47.8% versus 11.4%; odds ratio (OR) 7.436 (95% confidence interval (CI) 4.127, 13.401);  $p < 0.001$ ). The main secondary outcome of ASDAS-MI response at Week 52 was significantly higher with certolizumab versus placebo (47.2% versus 7.0%; OR 15.231 (95% CI 7.336, 31.623);  $p < 0.001$ ). The primary analysis results for both ASAS40 responses at Week 12 and ASDAS-MI at Week 52 were supported by similar findings from sensitivity analyses. Improvements, although not statistically powered, in ASAS 40 response were observed for the certolizumab group compared to placebo for all subgroups analysed. Response to certolizumab was numerically higher in certain subgroups of interest including younger subjects (< 45 years of age), male patients, those with shorter symptom duration (< 5 years), those who were both MRI and CRP positive (compared to only 1 of those variables being positive) and subjects with higher baseline SI joint Spondyloarthritis Research Consortium of Canada (SPARCC) scores (> 5).

Secondary efficacy endpoints were all statistically in favour of certolizumab compared with placebo, apart from the final outcome, including changes from baseline in BASDAI, BASFI, Ankylosing Spondylitis Quality of Life (ASQoL) and nocturnal spinal pain at Week 52 and ASAS40 at Week 52 (56.6% versus 15.8%; OR 7.359 (95% CI 4.286, 12.636);  $p < 0.001$ ). The supporting MRI evaluation showed statistically significant improvements in SI joint inflammation.

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<sup>2</sup> The ASAS Response Criteria (ASAS 40) is defined as an improvement of at least 40% and an absolute improvement of at least 10 units on a 0 to 100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI).

### **Study AS001**

Study AS001 was a Phase III randomised, double blind, multicentre, multinational, parallel group, placebo controlled trial which evaluated the efficacy and safety of certolizumab in 325 adults with active axial SpA (that is, both nr-axial SpA (n = 141) and ankylosing spondylitis). It was previously submitted in 2013 with 24 week double blind data but longer term data are now available up to Week 204. It examined two dosage regimens that included the same loading dose of 400 mg at Weeks 0, 2 and 4 and then either 200 mg Q2W or 400 mg Q4W compared to placebo as proposed by the sponsor in this submission. Half the study population had to fulfil both the mNY criteria for a definite diagnosis of AS and the ASAS criteria. The other half should not have met the mNY criteria but at least 50% of those patients had to meet the new ASAS imaging criteria, and the remainder could be enrolled based on meeting the ASAS clinical criteria only. Subjects were to be intolerant to, or have had an inadequate response to at least 1 NSAID (30 days at maximum dose or 2 weeks at maximum dose for 2 NSAIDs). The treatment groups and patient subsets were well balanced with respect to demographic and baseline disease characteristics with some expected differences noted between the AS and nr-axial SpA subgroups.

The primary efficacy variable of ASAS 20 response rate;<sup>3</sup> at Week 12 in the overall axial SpA population was statistically significantly greater ( $p < 0.004$  and  $p < 0.001$ ) in both certolizumab groups (57.7% with 200 mg Q2W and 63.6% with 400 mg Q4W) compared to placebo (38.3%). In the nr-axial SpA sub-population, the percentages of subjects with an ASAS 20 response at Week 12 was higher with certolizumab 200 mg Q2W (58.7%) and 400 mg Q4W (62.7%) compared to placebo (40.0%). At Week 24, the ASAS20 response was also greater with 200 mg Q2W (65.2%) and 400 mg Q4W (70.6%) compared to placebo (24.0%). Other efficacy endpoints are discussed in the clinical evaluation report. No consistent, clinically relevant differences in efficacy between the two certolizumab dosing regimens were observed. The open label period showed some efficacy data up to Week 204 however, a post-hoc analysis of ASAS 20 response showed a reduced response at the end (all certolizumab treated nr-axial SpA population was 63.4% at Week 24, 69.5% at Week 48 and 49.6% at Week 204).

### **Safety**

Safety is derived from the two Phase III studies and two supportive ongoing studies in axial SpA, including 182 nr-axial SpA subjects who received the 200 mg Q2W dose regimen for a mean 42.7 weeks in placebo controlled studies (Pool S1 of Study AS001; 24 weeks and Study AS0006; 52 weeks). In the Pool S2 dataset (ankylosing spondylitis and nr-axial SpA), a total of 680 subjects have been exposed to certolizumab 200 mg Q2W for a mean of 56.4 weeks. Approximately half of the patients in the dataset received concurrent disease-modifying anti-rheumatic drugs (DMARD), more than 75% were taking concomitant NSAIDs, and approximately 5% of all subjects had received prior anti-TNF treatment. The safety profile in adult patients with active nr-axial SpA was as expected for an anti-TNF therapy and was consistent with previous experience. Treatment emergent adverse events (AE) were higher on certolizumab than placebo in Pool S1 at 76.9% versus 64.7% and similar in Pool S2 at 69.7% of subjects in the all certolizumab 200 mg Q2W group and 70.9% of subjects in the all certolizumab group (200 mg Q2W and 400 mg Q4W). Infections were the most common AE recognised in the axial SpA studies, and these occurred at a higher frequency on certolizumab versus placebo (Pool S1; 51.6% versus 32.6% for infections and infestations). Most infections were mild in severity, self-limiting, and were predominately either upper respiratory tract infection (URTI) or

<sup>3</sup> The ASAS Response Criteria 20 (ASAS 20) is defined as an improvement of at least 20% and an absolute improvement of at least 10 units on a 0 to 100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI).

nasopharyngitis. Gastrointestinal AEs were also more common on certolizumab (Pool S1; 20.3% versus 10.2%). Treatment related AEs were higher on certolizumab compared with placebo (Pool S1; 30.8% versus 15.0%) with infection being the most common. The three most common types of infections (URTI, nasopharyngitis and oral herpes) occurred at 2 to 3 fold higher incidence with certolizumab. General disorders and administration site conditions were more common with certolizumab versus placebo (7.1% versus 2.1%), and this was mainly explained by the higher frequency of injection site reactions. Skin and subcutaneous tissue disorders were also more frequent. Injection site reactions (ISR) affected about 5% of certolizumab treated subjects in the axial SpA studies. Most ISRs were mild, resolved without specific intervention and did not result in permanent discontinuation. Five acute hypersensitivity reactions were reported with certolizumab.

Discontinuations due to AEs occurred at a low and similar frequency (1.6 to 5.0% versus 2.1%). During the 52 week reporting period of Pool S1, the incidence of serious adverse events (SAE) was low overall, but almost 2 fold higher with certolizumab (4.4%) versus placebo (2.7%). Two patients developed reactivation of latent TB, which had onset of about 4 to 5 months after commencing certolizumab and a patient experienced Legionella pneumonia and one patient developed oesophageal candidiasis. No deaths, major adverse cardiovascular events or cases meeting Hy's law;<sup>4</sup> were reported in the axial SpA studies. Two certolizumab subjects recorded optic neuritis in the axial SpA program. Four certolizumab patients developed malignancies in the axial SpA studies (versus 1 on placebo in Study AS0006). In Pool S1, hepatic AEs were higher on certolizumab than placebo (5.5% versus 2.7%) with most being increased alanine aminotransferase (ALT) and one patient who was reported as experiencing toxic hepatitis. Most patients with increases in liver function tests recorded mild to moderate severity changes, without associated clinical implications. Certolizumab treated subjects also recorded a higher frequency of new onset leukopaenia. Almost all certolizumab subjects in the new pivotal study recorded treatment emergent positive ADA results and neutralising activity was observed in 21.8% of ADA positive subjects. In the previous Phase III study, using a different, less sensitive assay methodology, the incidence of positive ADA was much lower at 9.6%.

### **Clinical evaluator's recommendation**

The clinical evaluator has recommended approval.

### **Risk management plan**

There was no requirement for a risk management plan (RMP) evaluation for a submission of this type.<sup>5</sup>

### **Risk-benefit analysis**

#### **Delegate's considerations**

##### ***Benefit/risk***

The ongoing pivotal study has demonstrated statistically significant and clinically meaningful improvements in efficacy in a dedicated population of patients with nr-axial SpA according to ASAS classification criteria for certolizumab 200 mg Q2W and with an acceptable safety profile up to 52 weeks of treatment that is consistent with the

<sup>4</sup> Hy's Law: alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN.

<sup>5</sup> The sponsor must still comply with routine product vigilance and risk minimisation requirements.

known safety profile of certolizumab. There is however, limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events, which will require further data. There are some significant identified safety concerns including the risk of serious infection, opportunistic infection (including cases of reactivated TB), injection related reactions, hypersensitivity reactions and neurological disorders such as optic neuritis. These safety concerns are consistent with the known profile of certolizumab in other approved treatment indications. The submission appears to generally adhere with the EU guidelines.

The pivotal study is supported by the previously submitted study in both ankylosing spondylitis and nr-axial SpA. The baseline demographic and disease related characteristics of patients in the Phase III studies are similar to those in the anticipated Australian patient cohort, and are therefore generalisable to the Australian context. The proposed indication includes objective signs of inflammation along with more detail in the Clinical Trials section, consistent with the EU indication. The Clinical Trials section also includes a definition of active disease. The proposed dosage includes a loading dose and maintenance dose which is supported by the pivotal study (200 mg Q2W), the currently approved indications of ankylosing spondylitis, rheumatoid arthritis and psoriatic arthritis and consistent with the EU approved dosage. The clinical evaluator has recommended approval.

#### ***Data deficiencies and outstanding issues***

The new pivotal study did not include the optional dosage regimen of 400 mg Q4W as requested by the sponsor, however this is supported by a small amount of data in the previous Phase III study that included nr-axial SpA (n = 51) and ankylosing spondylitis patients but examined two maintenance dose regimens (200 mg Q2W and 400 mg Q4W). This is also consistent with the current dosage regimen for other Cimzia indications and as approved in the EU for nr-axial SpA.

The new pivotal study required patients to have had an inadequate response to, had a contraindication to, or been intolerant to at least 2 NSAIDs, whereas the sponsor is requesting an indication for patients who have been intolerant or have had an inadequate response to at least one NSAID. For consistency with the EU indication and medicines approved in Australia for nr-axial SpA, it is recommended the indication be amended to patients '*who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs)*'.

The pivotal study included patients with moderate-severe axial SpA activity however, the EU indication is restricted to severe disease only. The US indication has not been restricted by severity and the sponsor has also not requested it be restricted. Both golimumab and etanercept registered here are not restricted by disease severity. The clinical evaluator has not recommended it be restricted.

For subjects who developed ADA positive results in both axial SpA trials, the clinical relevance for safety outcomes is unclear. However, the development of anti-certolizumab antibodies may be associated with a lack or loss of efficacy. No population PK analysis was provided but the sponsor provided a graphical evaluation of the degree to which ADA titre and subject weight influences certolizumab concentrations in Study AS0006, showing significantly lower certolizumab concentrations in the heaviest weight quartile and subjects with high titre ADA.

Certolizumab has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction, and in those with concurrent hepatitis B or C virus or human immunodeficiency virus (HIV). Populations with inadequate clinical data regarding certolizumab therapy are identified in the current RMP. There is also limited data in patients with prior anti-TNF exposure.

There is limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events.

### **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 to be positive and recommends approval for the indication:

#### *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).*

### **Conditions of registration**

The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:

- The final study report for Study AS0006.

### **Summary of issues**

The primary issues with this submission are as follows:

1. The Advisory Committee on Prescription Medicines (ACPM);<sup>6</sup> identified concerns with the previous submission for nr-axial SpA that primarily related to diagnostic criteria and objective signs of inflammation.
2. The approved EU indication is restricted to patients with severe disease however the sponsor is not requesting this restriction here. The US indication does not include this restriction.
3. The sponsor has proposed specific objective signs of inflammation to be included in the indication, consistent with the EU approved indication. The US indication does not specify them in the indication but refers to them in the Clinical Trials section. The same detail is also proposed for inclusion in the Australian PI Clinical Trials section.

### **Proposed action**

The Delegate has no reason to say, at this time, that the application for Cimzia should not be approved for registration, pending further advice from ACM.

### **Request for Advisory Committee on Medicines advice**

The committee is requested to provide advice on the following specific issues:

1. Have the concerns previously identified by the committee been adequately addressed in this re-submission?
2. What are the committee's views on whether the proposed indication should only be for patients with severe disease?
3. What are the committee's views on the description of the objective signs of inflammation?

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<sup>6</sup> The ACPM is the precursor committee to the ACM; see footnote 7 (below) for further details.

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.

### **Advisory Committee Considerations<sup>7</sup>**

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Cimzia single use, pre-filled syringe and pen, containing 200 mg/mL of 1 mL volume of certolizumab pegol.

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

#### *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).*

### **Specific advice**

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

**1. *Have the concerns previously identified by the committee been adequately addressed in this re-submission?***

The ACM was of the opinion that Study AS0006 has provided clear evidence of the efficacy of Cimzia in a cohort of patients more clearly defined by MRI and CRP. Although this study is ongoing, the ACM agreed that the evidence from this study was sufficient to allay previous concerns.

**2. *What are the committee's views on whether the proposed indication should only be for patients with severe disease?***

The ACM noted that Study AS0006 includes patients with moderate to severe nr-axSpA and that there is evidence that the efficacy of Cimzia is better in patients with less severe disease. Thus, the ACM was of the view that the proposed indication should not be limited by the severity of the disease.

**3. *What are the committee's views on the description of the objective signs of inflammation?***

The ACM was of the view that the description of the objective signs of inflammation in the proposed indication are sufficient and that further specification is not required, particularly for MRI criteria as this is a rapidly evolving field. The ACM advised that details regarding objective signs of inflammation (for example, the definition of 'elevated' CRP levels) could be included in the PI.

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<sup>7</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 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.



### **General advice**

The ACM advised that the indications should be restricted to patients that have failed at least two NSAIDs, rather than one as initially proposed. This is consistent with the inclusion criteria for Study AS0006, and indications for other drugs for nr-axSpA.

### **Outcome**

Based on a review of quality, safety and efficacy, the TGA approved the registration of Cimzia (certolizumab pegol (rbe)) solution for injection, for the following extension of indications:

#### *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).*

As such, the full indications at this time were:

#### **Rheumatoid arthritis**

*Cimzia is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients.*

- *Combined with MTX in case of either an inadequate response or intolerance to previous therapy with one or more disease modifying antirheumatic drugs (DMARDs) or*
- *As monotherapy in case of a contraindication or intolerance to MTX (see Section 4.2 Dose and Method of Administration).*

*Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.*

*Cimzia in combination with MTX is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs.*

#### **Psoriatic arthritis**

*Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease modifying antirheumatic drug therapy (DMARDs) has been inadequate. Cimzia has been shown to improve physical function.*

#### **Ankylosing spondylitis**

*Cimzia is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).*

#### **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).*

#### **Plaque psoriasis**

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

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

- This approval does not impose any requirement for the submission of Periodic Safety Update Reports (PSURs). 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.
- The following study report must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission:
  - The final study report for Study AS0006.
- For all injectable products the Product Information must be included with the product as a package insert.

## **Attachment 1. Product Information**

The PI for Cimzia 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**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605  
<https://www.tga.gov.au>