

**7.10 CERTOLIZUMAB PEGOL,  
Injection 200 mg in 1 mL pre-filled syringe/pen,  
Cimzia<sup>®</sup>,  
UCB Australia Proprietary Limited**

**1 Purpose of Application**

- 1.1 The minor resubmission requested the PBAC reconsider the basis of its March 2019 recommendation of certolizumab pegol (CZP) for the treatment of patients with chronic plaque psoriasis (CPP). Specifically, the resubmission requested a change in the equi-effective dose for CZP from the previously recommended 400 mg once every two weeks to a dose of 200 mg or 400 mg every two weeks.

**2 Requested listing**

- 2.1 The requested listings for CZP were broadly consistent with other listings for biologics for the treatment of CPP, with separate listings proposed for the 200 mg every two weeks dose regimen (herein referred to as CZP 200 mg) and 400 mg every two weeks dose regimen (herein referred to as CZP 400 mg). The resubmission proposed specific restrictions for use of CZP 400 mg in patients who either previously had an inadequate response to CZP 200 mg or who weigh  $\geq 90$  kg (Table 1).

**Table 1: Summary of essential elements of the requested listing**

	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	DPMQ
Certolizumab pegol 200 mg/mL injection, 2 x 1 mL (pen devices and syringes)				
INITIAL (LOADING DOSE)	3	6	0	\$3,008.50
INITIAL (CZP 200 mg)	1	2	3	\$1,014.76
INITIAL (CZP 400 mg, for patients that weigh ≥ 90 kg)	2	4 <sup>2</sup>	3	\$2,024.35 <sup>1</sup>
CONTINUING (CZP 200 mg)	1	2	5	\$1,014.76
CONTINUING (CZP 400 mg)	2	4 <sup>2</sup>	5	\$2,024.35 <sup>1</sup>

CZP certolizumab pegol; DPMQ dispensed price for maximum quantity

1. DPMQ in resubmission was incorrectly reported as \$2,029.52.

2. Maximum quantity (units) in resubmission was incorrectly reported as 2.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### 3 Background

#### **Registration and PBS listing status**

- 3.1 CZP was registered by the TGA on 29 May 2019 for the treatment of adult patients with moderate to severe CPP who are candidates for systemic therapy or phototherapy.
- 3.2 The recommended dose of CZP for CPP is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially (week 0) and at weeks 2 and 4 followed by 200 mg or 400 mg every 2 weeks. A dose of 400 mg every 2 weeks may be specifically considered in patients with an insufficient response to 200 mg every 2 weeks or in patients with a body weight ≥ 90 kg. At the time of PBAC consideration in March 2019, the TGA Delegate's Overview supported a dose of CZP of 400 mg every two weeks in the maintenance phase, with 200 mg every two weeks as an alternative dose and the Advisory Committee on Medicines supported a dose of 200 – 400mg every two weeks.
- 3.3 CZP is currently listed on the PBS as a General Schedule, written Authority Required listing for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The dose for the currently listed indications is 400 mg at weeks 0, 2 and 4 followed by a maintenance dose of 200 mg every two weeks or 400 mg every four weeks.

#### **Previous PBAC consideration**

- 3.4 At its March 2019 meeting, the PBAC recommended the Authority Required listing of CZP on a cost- minimisation basis with the least costly biologic for CPP. In making this recommendation, the PBAC accepted any of the current PBS listed biologics for CPP could be an alternative therapy to CZP. The PBAC considered the equi-effective doses of CZP at a dose of 400 mg every 2 weeks and alternative biologics could be derived from the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets. The PBAC previously considered CZP 200 mg should be

priced on the same per mg basis as CZP 400 mg (paragraphs 7.1, 7.2, 7.8, CZP Public Summary Document (PSD), March 2019 PBAC meeting).

3.5 A summary of the previous major submission and the current minor resubmission is provided in Table 2.

**Table 2: Summary of the previous submission and the current resubmission**

	<b>March 2019 submission</b>	<b>Current resubmission</b>
Requested PBS listing	Written authority required listing for CPP, consistent with other biologic listings for CPP. The submission requested listing for CZP 200 mg only (i.e. 400 mg, given as 2 x 200 mg injections, at week 0, 2 and 4 followed by 200 mg every 2 weeks).	The resubmission requested listing for CZP 200 mg and CZP 400 mg (i.e. 400 mg, given as 2 x 200 mg injections, at week 0, 2 and 4 followed by 200 mg or 400 mg every 2 weeks).  Initial treatment with CZP 400 mg (after the loading dose) is restricted to patients weighing ≥ 90 kg.  The resubmission requested consideration for patients to be able to up-titrate from CZP 200 mg to CZP 400 mg for non-response.
Requested effective DPMQs	Requested the current DPMQ of certolizumab pegol: <ul style="list-style-type: none"> <li>• AEMP [200 mg/2 pack] \$ [REDACTED]</li> <li>• DPMQ [loading dose] \$ [REDACTED]</li> <li>• DPMQ [CZP 200 mg] \$ [REDACTED]</li> </ul>	Unchanged, but added new proposed DPMQs for CZP 400 mg: <ul style="list-style-type: none"> <li>• AEMP [200 mg/ 2 pack] \$ [REDACTED]</li> <li>• DPMQ [loading dose] \$ [REDACTED]</li> <li>• DPMQ [CZP 200 mg] \$ [REDACTED]</li> <li>• DPMQ [CZP 400 mg] \$ [REDACTED]</li> </ul>
Comparator	The submission nominated ADA and UST as the main comparators.  PBAC considered all PBS listed biologic therapies for CPP are alternative therapies and could be substituted by CZP [paragraph 7.4].	Unchanged.
Dosage recommendation in Product Information	Recommended by TGA Delegate: 400 mg every two weeks in the maintenance phase, with 200 mg every two weeks as an alternative dose. Recommended by ACM: 200-400 mg every two weeks	Approved: the maintenance dose is CZP 200 mg or CZP 400 mg. A dose of CZP 400 mg may be specifically considered in patients with an insufficient response to CZP 200 mg or in patients with a body weight of 90 kg and above.
Clinical evidence	Indirect comparison of CZP 200 mg versus UST or ADA with placebo as common reference.  Comparisons with CZP 400 mg undertaken during the evaluation.  Direct comparison with ETN not included in submission but undertaken during evaluation.	Unchanged, no new clinical evidence presented.
Key effectiveness data	Comparison of PASI 75 response at 12 or 16 weeks.	Unchanged
Clinical claim	Claim of non-inferiority in terms of both effectiveness and safety compared to UST and ADA. PBAC was satisfied non-inferiority to UST and ADA demonstrated for CZP 200 mg and CZP 400 mg [paragraph 7.6].	Unchanged

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	March 2019 submission	Current resubmission
Economic evaluation	Requested same price as current CZP listings for 200 mg strength.  PBAC considered cost minimisation to least costly biologic for CPP was appropriate and CZP 200 mg should be priced on the same per mg basis as CZP 400 mg [paragraphs 7.7/7.8]	The resubmission presented a cost minimisation analysis of CZP 200 mg vs UST and ADA over 2 years incorporating induction and maintenance doses. The resubmission proposed a RSA to ensure the cost of CZP 400 mg is no higher than CZP 200mg.
Number of prescriptions	Submission assumed CZP 200 mg would substitute for other biologics and would not grow the market  Estimated 882 scripts in year 1, increasing to 3,991 in year 6.	Amended estimates provided incorporating CZP 200 mg and CZP 400 mg.  Estimated 585 scripts in year 1, increasing to 3,251 in year 6.
Estimated net cost to PBS	\$447,011 saving in year 1 increasing to a saving of \$2,181,499 in year 6.	\$296,029 saving in year 1, increasing to a saving of \$1,967,636 in year 6.  The resubmission assumed 13.2% of initial scripts will be for CZP 400 mg due to patients weighing ≥ 90 kg. The resubmission further assumes 7.3% of patients will up-titrate to CZP 400 mg due to insufficient response.
Risk sharing arrangement	None	The Sponsor proposed a RSA to rebate the Commonwealth the cost of additional doses for patients who used CZP 400 mg.

ACM Advisory Committee on Medicines; ADA adalimumab; AEMP approved ex-manufacturer price; CPP chronic plaque psoriasis; CZP certolizumab pegol; DPMQ dispensed price for maximum quantity; ETN etanercept; PASI Psoriasis Area Severity Index; PBAC Pharmaceutical Benefits Advisory Committee; PBS Pharmaceutical Benefits Scheme; RSA risk sharing arrangement; TGA Therapeutic Goods Administration; UST ustekinumab

Source: Compiled during the evaluation. Paragraph references for March 2019 refer to the CZP public summary document.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## 4 Comparator

- 4.1 The previous major submission considered by the PBAC in March 2019 nominated ustekinumab (UST) and adalimumab (ADA) as the primary comparators, and the PBAC considered all PBS-listed biologics for CPP could be considered alternative therapies.
- 4.2 The *National Health Act 1953*, Section 101(3B) stipulates that if the requested treatment is substantially more costly than alternative therapies, then the PBAC could only recommend listing at a higher price, if it is satisfied that the treatment provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the existing therapies. The PBAC previously advised there was no evidence to support a claim that CZP provided a significant improvement in efficacy or reduction in toxicity compared to any of the currently PBS listed biologics for severe CPP (paragraph 7.6, CZP PSD, March 2019).

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## 5 Consideration of the evidence

### ***Sponsor hearing***

5.1 There was no hearing for this item as it was a minor submission.

### ***Consumer comments***

5.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical trials***

5.3 The resubmission summarised evidence previously considered by the PBAC and did not present any new clinical evidence.

5.4 The resubmission presented information on the proportion of patients in the clinical studies that underwent a protocol-driven dose escalation from CZP 200 mg to CZP 400 mg. Across three studies, 18% to 34% of patients treated with CZP 200 mg did not achieve a Psoriasis Area Severity Index (PASI) 75 response at 16 weeks and 10% to 20% increased to CZP 400 mg using a less stringent PASI 50 definition. No evidence was presented to demonstrate that patients who do not respond to CZP 200 mg subsequently respond to treatment with CZP 400 mg.

### ***Clinical claim***

5.5 The PBAC previously considered the claim of non-inferior effectiveness and safety of both CZP 200 mg and CZP 400 mg was supported versus UST and ADA (paragraph 7.6, CZP PSD, March 2019). The PBAC considered that while the clinical need for an additional treatment with a mechanism of action the same as several other listed biologics (tumour necrosis factor- $\alpha$  inhibitor) was low, the PBAC noted there may be advantages for patients who are either pregnant or intending to become pregnant as it is unlikely to cross the placenta (paragraph 7.3, CZP PSD, March 2019).

### ***Other clinical issues***

5.6 The resubmission argued the equi-effective doses should be 200 mg or 400 mg every two weeks as this reflects the dose regimen for CPP in the TGA approved Product Information (PI).

5.7 The resubmission argued that consistent with the approved PI, the maintenance dose of CZP for adult patients with plaque psoriasis is CZP 200 mg or CZP 400 mg, with the higher dose specifically considered in patients weighing  $\geq 90$  kg or patients with insufficient response to CZP 200 mg.

5.8 The resubmission argued patients should have the capacity to up-titrate to CZP 400 mg if they have an inadequate response to CZP 200 mg. In March 2019 the PBAC considered that CZP 400 mg was most likely to be used in practice as patients could only fail a maximum of 3 biologic agents in a five year period, therefore clinicians and

patients were likely to use a higher dose to ensure the best opportunity of a response to treatment. The resubmission specifically requests the ability for patients to up-titrate from CZP 200 mg to CZP 400 mg. However, under current restrictions, inadequate response on CZP 200 mg would be considered a treatment failure and patients would be required to cease therapy and this would count as one of three allowable treatment failures in the treatment cycle. There is no provision in current CPP restrictions for other biologics for patients to up-titrate due to lack of response. The pre-PBAC response indicated the sponsor was willing to list CZP 200 mg with weight based dosing for those over 90 kg. As per the PI, all patients commence on 200 mg and dose escalation can occur where needed for those patients >90kg. The PI also allows for dose escalation: a dose of 400 mg every 2 weeks may be specifically considered in patients with an insufficient response to 200 mg every 2 weeks.

### **Economic analysis**

- 5.9 The resubmission requested the same price as the March 2019 submission, i.e. the listed price of CZP for other listed indications. A comparison of the cost of CZP 200 mg, ADA and UST (both using the published price) over 2 years was presented, with the resubmission noting that based on this analysis it could claim a higher price than requested. The PBAC has previously recommended CZP should be cost-minimised to the lowest cost alternative biologics (paragraph 7.7, CZP PSD, March 2019).
- 5.10 The resubmission argued the equi-effective doses should be 200 mg or 400 mg every two weeks compared with alternative therapies, with pricing based on a 200 mg every two weeks dosage regimen.
- 5.11 The resubmission proposed a risk sharing agreement (RSA) (also referred to in the resubmission as a special pricing agreement) to rebate back the cost of the additional 200 mg dose required for CZP 400 mg in anyone that uses it beyond the loading dose.

### **Drug cost/patient/year: \$ [REDACTED] (CZP 200 mg).**

- 5.12 The estimated drug cost (dispensed) per patient per year for CZP 200 mg including the loading dose is \$ [REDACTED]. The resubmission noted this is a lower cost per patient per year than for UST and ADA but acknowledged the prices for UST and ADA were based on published prices.
- 5.13 The estimated drug cost (dispensed) per patient per year for CZP 400 mg including the loading dose is \$ [REDACTED] (before rebate), noting the resubmission has proposed an RSA with the intention to rebate the cost of the additional 200 mg vial required for patients who require this dose.

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

- 5.14 The minor resubmission estimated a net save to the PBS of less than \$10 million in Year 6 of listing, with a total net save to the PBS of less than \$10 million over the first 6 years of listing. The predicted saving is driven by substitution of more costly

alternative biologics and is based on published prices. It is likely that listing CZP for CPP based on a cost-minimisation basis with the least costly biologic using effective prices would be cost-neutral to the PBS.

- 5.15 The updated utilisation estimates in the minor resubmission assumed CZP would substitute for adalimumab, ustekinumab, secukinumab, ixekizumab and etanercept.
- 5.16 The minor re-submission estimated 13.2% of patients would weigh 90 kg or more and that 100% of these would initiate and continue on CZP 400 mg, based on the following assumptions:
- 70% of use of CZP will be in females (based on utilisation in rheumatoid arthritis) and most of these patients will be women of child-bearing age. The submission assumed no female patients will weigh 90 kg or more and will not be prescribed CZP 400 mg.
  - Of the 30% of use in males, the resubmission estimated 13.2% of the population weigh 90 kg or more, using the average of estimates from Australian Bureau of Statistics data (9.8%) and Australian psoriasis registry data (16.53%).
- 5.17 The PBAC noted that according to data provided in the minor resubmission, 55% of males and 32% of females treated with biologics in the Australian Psoriasis Registry weighed  $\geq 90$  kg and considered the assumption that 13.2% of patients would weigh  $\geq 90$  kg was likely an underestimate. The PBAC noted the average weight of patients in the pivotal clinical trials for CZP was 91 kg which also supported 13.2% being an underestimate.
- 5.18 The resubmission estimated 7.3% of patients would require up-titration to CZP 400 mg due to inadequate response, based on Australasian psoriasis registry data, which indicated 7.3% of patients required dose escalation amongst currently-listed biologics for CPP. In the pivotal clinical trials, 18% to 34% of patients treated with CZP 200 mg did not achieve a PASI75 response at 16 weeks therefore, 7.3% may be an underestimate.
- 5.19 As a minor submission, the financial estimates were not independently evaluated.

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

- 5.20 The resubmission proposed a RSA to rebate the Commonwealth the cost of the additional 200 mg dose for all patients who use CZP 400 mg after the loading dose, with the intention of there being no additional cost to the PBS for any patients who use the higher dose regimen compared to CZP 200 mg.
- 5.21 The resubmission proposed separate listings for CZP 400 mg to facilitate management of the proposed RSA.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## **6 PBAC Outcome**

- 6.1 The PBAC did not advise that a change should be made to its previous recommendation for certolizumab pegol (CZP) for the treatment of chronic plaque psoriasis (CPP). The PBAC reaffirmed its March 2019 recommendation that CZP 400 mg should be listed on a cost minimisation basis with the least costly alternative biologic for this indication and that it would be appropriate to price CZP 200 mg on the same per mg basis as CZP 400 mg.
- 6.2 The PBAC noted the submission argued that most patients would be treated with CZP 200 mg, and CZP 400 mg would only be used by patients who: (1) weigh  $\geq 90$  kg, and (2) do not achieve an adequate response to treatment with CZP 200 mg. The PBAC noted the resubmission estimated approximately 13.2% of the treated population would use CZP 400 mg for patients weighing  $\geq 90$  kg, and a further 7.3% of patients would move to CZP 400 mg following inadequate response to CZP 200 mg. The PBAC considered the assumptions regarding the proportion of use of CZP 400 mg to be underestimated for the reasons outlined in paragraphs 5.17 and 5.18.
- 6.3 The PBAC noted that documenting inadequate response on CZP 200 mg in order to be prescribed CZP 400 mg would be considered a treatment failure and this would count as one of three allowable treatment failures in the treatment cycle. The PBAC noted no evidence was presented in the resubmission to support the claim that patients who do not respond to CZP 200 mg will respond to CZP 400 mg. The PBAC considered this supported its previous consideration that a majority of patients would be treated with CZP 400 mg to provide the best chance of achieving an adequate response (paragraph 7.6, CZP PSD, March 2019 PBAC meeting).
- 6.4 While the submission argued only two specific populations were likely to be treated with CZP 400 mg, the PBAC considered it was likely to be used more broadly as clinicians would choose the regimen with the best chance of achieving an adequate response for the majority of patients. The PBAC recalled CZP 400 mg consistently had better response rates compared to CZP 200 mg, UST and ADA (Table 5, CZP PSD, March 2019 PBAC meeting) and therefore considered the majority of patients were likely to receive CZP 400 mg.
- 6.5 The PBAC noted the financial estimates provided in the resubmission were based on the published prices of the alternative biologics. The PBAC considered that if CZP (at a dose of 400 mg every 2 weeks) was listed on the PBS on the basis of cost-minimisation to the lowest cost alternative biologic the listing would be cost-neutral to the PBS.
- 6.6 The PBAC noted the Sponsor proposed separate listings for CZP 200 mg and CZP 400 mg with the requested price for CZP 200 mg the same as the current listed price of CZP 200 mg. The Sponsor proposed providing rebates via a special pricing arrangement for use of the 400 mg dose, with the intent that patients being treated with CZP 400 mg would cost no more than patients being treated with CZP 200 mg. Given its view that the majority of patients were likely to receive CZP 400 mg, the PBAC

considered the submission's proposal for pricing of CZP to be based on the 200 mg dosing regimen to be inappropriate.

- 6.7 The PBAC noted the dose for CZP in the approved product information was different to that proposed by the TGA Delegate and recommended by the ACM at the time of its previous consideration of CZP (paragraph 3.2). Based on the approved dose regimen and its previous acceptance that CZP 200 mg and CZP 400 mg were non-inferior to UST and ADA (paragraph 5.5), the PBAC considered it may be reasonable for the equi-effective dose of CZP for the purpose of a cost minimisation analysis against the least costly alternative biologic to be based on a split between 200 mg or 400 mg (with 400 mg being the majority of use) every 2 weeks. However, in the absence of reliable estimates of this split (noting the submission's significant underestimation of 400 mg use), the PBAC was not minded to change its March 2019 advice. Further, the PBAC noted that the implementation of a special pricing arrangement as proposed in the resubmission was not adequately substantiated.
- 6.8 The PBAC reaffirmed its view that the clinical need for an additional treatment with a mechanism of action the same as multiple other listed biologics for CPP was low, but CZP may offer an advantage for patients who are either pregnant or intending to become pregnant.
- 6.9 The PBAC reaffirmed its advice from March 2019 relating to interchangeability with alternative biologics for CPP, nurse practitioner prescribing and the Early Supply Rule remained appropriate. The PBAC considered it was reasonable to add risankizumab (recommended for CPP in July 2019) to the list of medicines considered interchangeable with CZP.
- 6.10 The PBAC noted the flow-on restriction changes identified in the March 2019 recommendation to include certolizumab pegol to the notes in other listings to include CZP in the list of therapies for CPP remained appropriate.
- 6.11 The PBAC noted that this submission is not eligible for an Independent Review as the resubmission is not for an entirely different disease or condition than the disease or condition for which the medicine is already subsidised/recommended, an objectively different subtype of disease, or targeting a different population or stage of disease.

**Outcome:**

Rejected

## **7 Context for Decision**

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

in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **8 Sponsor's Comment**

UCB is disappointed with the outcome of the Nov 2019 PBAC meeting and will continue to work with the Department to make Cimzia available for the treatment of CPP.