

**5.15 ADALIMUMAB,
Injection 40 mg in 0.4 mL pre-filled pen
Injection 40 mg in 0.4 mL pre-filled syringe
Injection 80 mg in 0.8 mL pre-filled syringe
Ardalicip[®],
Cipla Australia Pty Ltd**

1 Purpose of Submission

- 1.1 The Category 3 submission sought to list a new biosimilar brand of adalimumab (Ardalicip[®]) in the forms of 40 mg in 0.4 mL pre-filled pen (PFP), 40 mg in 0.4 mL pre-filled syringe (PFS) and 80 mg in 0.8 mL PFS under the same circumstances as the PBS-listed reference biologic Humira[®].

2 Background

Registration status

- 2.1 Ardalicip was TGA registered on 6 September 2022 and was determined to be a biosimilar to the reference brand Humira. Ardalicip 40 mg and 80 mg are approved for the same indication as Humira 40 mg and 80 mg.

Previous PBAC consideration

- 2.2 Ardalicip has not previously been considered by the PBAC.

3 Requested listing

- 3.1 The submission requested listing Ardalicip under the same circumstances as the PBS-listed reference biologic Humira 40 mg in 0.4 mL PFS, 40 mg in 0.4 mL PFP and 80 mg in 0.8 mL PFS. Ardalicip 80 mg in 0.8 mL PFS will be the first biosimilar brand for this form and strength of adalimumab.
- 3.2 The PBAC was asked to advise whether biosimilar uptake drivers which currently apply to Amgevita, Hadlima, Hyrimoz, Idacio and Yuflyma including the different authority requirements for subsequent continuing treatment with the reference and biosimilar brands and inclusion of an administrative note encouraging the use of biosimilar brands for treatment naïve patients, should apply to Ardalicip if it is recommended for listing.
- 3.3 The PBAC was asked to advise, under Section 101(4AACD) of the Act whether, in the Schedule of Pharmaceutical Benefits:

- Humira, Yuflyma and Ardalicip PFS should be treated as equivalent to each other; and Humira, Yuflyma and Ardalicip PFP should be treated as equivalent to each other for the purposes of substitution (i.e. 'a' flagged in the schedule)
- 40 mg in 0.4 mL Ardalicip PFP and 40 mg in 0.8 mL Amgevita, Hadlima, Hyrimoz and Idacio PFP should be treated as equivalent to each other for the purposes of substitution (i.e. 'a' flagged in the schedule)
- 40 mg in 0.4 mL Ardalicip PFS and 40 mg in 0.8 mL Amgevita, Hadlima, Hyrimoz and Idacio PFS should be treated as equivalent to each other for the purposes of substitution (i.e. 'a' flagged in the schedule)

3.4 The requested restrictions are complex due to the number of items and indications required for the listing. If recommended by the PBAC, the implementation of these listings may occur across separate stages. As the submission requested the same restrictions as the reference brand, the full restrictions have not been reproduced here.

3.5 The summary of the listing follows:

Name, restriction, manner of administration, form	Max. Qty (packs)	Max. Qty (units)	No. of repeats	PBS item code	Proprietary name and manufacturer
ADALIMUMAB adalimumab 40 mg/0.4 mL injection, pre-filled pen	1	2	2	12345R	Ardalicip® Cipla Australian Pty Ltd
ADALIMUMAB adalimumab 40 mg/0.4 mL injection, pre-filled syringe	1	2	2	12338J	Ardalicip® Cipla Australian Pty Ltd
ADALIMUMAB adalimumab 80 mg/0.8 mL injection, pre-filled syringe	3	3	0	12372E	Ardalicip® Cipla Australian Pty Ltd

The sponsor has requested the same number of items and indications as Humira 40 mg in 0.4 mL and 80 mg in 0.8 mL. Maximum quantity packs and units and number of repeats will change to match the item code and indication. The example indication used is "Severe Crohn disease Treatment Phase: Initial treatment - Initial 1 (new patient)".

4 Comparator

4.1 The submission nominated the reference brand of adalimumab, Humira, as the main comparator. The PBAC considered that this was appropriate.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from one individual and one organisation via the Consumer Comments facility on the PBS website.
- 5.3 The PBAC noted the comments from the individual, which described a range of benefits of treatment with adalimumab for hidradenitis suppurativa, including improvement in symptoms and reduction in surgeries. The individual also noted that the availability of higher dosage forms on the PBS improves the affordability and accessibility of this medication for people who require higher doses.
- 5.4 The PBAC noted the advice received from the National Paediatric Medicines Forum (NPFC) which stated that adalimumab is highly utilised in the paediatric setting for inflammatory bowel disorders and juvenile idiopathic arthritis. The PBAC noted the NPFC's request that the listing of adalimumab should not have age limit restrictions to allow for prescribers to equitably prescribe to patients of all ages that meet the relevant criteria.

Clinical trials

- 5.5 The submission presented the following clinical studies. As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

Table 1: Studies presented in the submission

Trial ID	Protocol/Publication title	Study Objectives (Related to Safety)	Study Drug and Dose	No. of Subjects/ Patients Assigned to Treatment
AVT02-GL-100	Single Centre, Randomised, Single-Blind, Pilot Study to Compare the Safety, Tolerability and Pharmacokinetics of AVT02 to EU-approved Humira® as a Single Dose (40 mg) Subcutaneous Injection in Healthy Adult Subjects (ALVOPAD)	Primary: To evaluate the safety and tolerability of AVT02 and, EU-Humira administered as a single subcutaneous injection in healthy adult subjects. Secondary: Examine pharmacokinetics and immunogenicity.	AVT02 – 40mg/0.4mL prefilled syringe, administered as a single subcutaneous injection EU-Humira – 40mg/0.4mL prefilled syringe, administered as a single subcutaneous injection	24 healthy subjects
AVT02-GL-101	Multicenter, Randomized, Double Blind, 3-Arm, Parallel Study to Compare the Pharmacokinetics, Safety and Tolerability of AVT02 to EU-approved and US-licensed Humira® Administered as a Single Dose (40 mg Subcutaneous Injection)	Primary: To compare the PK of AVT02 with EU-Humira and US-Humira, and the PK of EU-Humira and US-Humira following a single 40 mg SC injection in healthy adult subjects. Secondary: Safety and tolerability of AVT02 vs EU/US-Humira.	AVT02 – 40mg/0.4mL prefilled syringe, administered as a single subcutaneous injection EU-Humira – 40mg/0.4mL prefilled syringe, administered as a single subcutaneous injection	392 healthy subjects

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	in Healthy Adult Volunteers (ALVOPAD FIRST)		EU-Humira – 40mg/0.4mL prefilled syringe, administered as a single subcutaneous injection	
AVT02-GL-301	A Multicenter, Double-blind, Randomized, Parallel group, Active Control Study to Compare the Efficacy, Safety, and Immunogenicity of AVT02 Versus Humira® in patients with Moderate to Severe Chronic Plaque Psoriasis (ALVOPAD PS)	<p>Primary: The primary objective was to assess the equivalence by Psoriasis Area and Severity Index (PASI) of AVT02 to European Union EU-Humira with regards to efficacy at Week 16 in subjects with moderate to severe chronic plaque psoriasis.</p> <p>Secondary: Efficacy of AVT02 and EU-Humira at weeks 8, 12, 16, 24, 32, 41, 50. Safety, tolerability, immunogenicity, and steady-state PK</p>	<p>AVT02 – Initial loading dose of 80 mg (2 × 40 mg) followed by 40mg/0.4mL EOW starting 1 week after the loading dose administered SC</p> <p>EU-Humira – Initial loading dose of 80 mg (2 × 40 mg) followed by 40mg/0.4mL EOW starting 1 week after the loading dose administered SC</p>	538 patients with chronic moderate to severe plaque psoriasis
AVT02-GL-102	Multicenter, Randomized, Open-Label, 2-Arm Parallel Study to Compare the Pharmacokinetics, Safety and Tolerability of AVT02 Administered Subcutaneously via Prefilled Syringe or Autoinjector in Healthy Adult Volunteers (ALVOPAD PEN)	<p>Primary: To compare the PK of a 40 mg SC dose of AVT02 administered either manually via PFS or via an AI, in healthy adult subjects.</p> <p>Secondary: Safety, tolerability, and immunogenicity of a 40 mg SC dose of AVT02 administered either manually via PFS or via an AI, in healthy adult subjects.</p>	<p>AVT02 – 40mg/0.4mL PFS, administered as a single SC injection</p> <p>AVT02 – 40mg/0.4mL prefilled AI, administered as a single SC injection</p>	207 healthy subjects
AVT02-GL-303	PRIMARY CLINICAL STUDY REPORT FOR AVT02-GL-303 Assessment of Real-life Patient Handling Experience of AVT02 Administered Subcutaneously with an Autoinjector in Patients with Moderate to Severe Active Rheumatoid Arthritis: An Open-label, Interventional, Single-arm Clinical Trial, followed by an Extension Phase of	<p>Primary: To assess the real-life subject handling experience with the use of an autoinjector in subjects with moderate to severe active rheumatoid arthritis who self-injected AVT02 SC.</p> <p>Secondary: Identify AI handling events, safety of repeated use.</p>	AVT02 – 40mg/0.4mL prefilled AI, administered as a single SC injection	106 patients with active rheumatoid arthritis

	AVT02 Administered with a Prefilled Syringe (ALVOPADPEN)			
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5.6 Some of the studies (AVT02-GL-101, AVT02-GL-102 and AVT02-GL-301) were presented in the TGA submission to register Ardalicip as a biosimilar to Humira.

Clinical claim

5.7 The submission claimed that Ardalicip is a biosimilar of Humira. The PBAC noted that the TGA Clinical Evaluation Report supported this claim.

5.8 The PBAC considered that the claims of non-inferior comparative effectiveness and safety compared to Humira were reasonable.

Estimated PBS usage and financial implications

5.9 The submission stated that Ardalicip is expected to substitute for Humira or the other biosimilar brands of adalimumab. The submission stated that the listing is not expected to grow the market for adalimumab, and therefore would be cost-neutral to Government.

6 PBAC Outcome

6.1 The PBAC recommended the Authority Required listing of adalimumab (Ardalicip) in the form of 40 mg in 0.4 mL PFS and PFP and 80 mg in 0.8 mL PFS as biosimilar brands of Humira on the General Schedule (Section 85) and Section 100 (Highly Specialised Drugs Program) for the following indications:

- Severe Crohn disease
- Moderate to severe ulcerative colitis
- Severe active juvenile idiopathic arthritis
- Complex refractory fistulising Crohn disease
- Severe active rheumatoid arthritis
- Severe psoriatic arthritis
- Ankylosing spondylitis
- Severe chronic plaque psoriasis
- Moderate to severe hidradenitis suppurativa

6.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Ardalicip PFP and PFS would be acceptable if it were cost-minimised to the lowest cost adalimumab brand.

6.3 The PBAC advised the equi-effective doses to be 1 mg of Ardalicip = 1 mg of Humira and all other biosimilar brands and formulations of adalimumab.

- 6.4 The PBAC considered that the claim of biosimilarity for Ardalicip compared to Humira was reasonably supported by the data. The PBAC noted the TGA Delegate's view that Ardalicip is biosimilar to Humira and that there were no clinically meaningful differences in the comparative pharmacology, pharmacokinetic and toxicity studies.
- 6.5 The PBAC considered that biosimilar uptake drivers should be applied to Ardalicip, consistent with the current PBS listings for adalimumab biosimilar brands, including:
- Authority Required listing of Ardalicip, with the Authority type for each treatment phase and indication to be consistent with current listings for the other biosimilar brands of adalimumab.
 - The application of the 'Biosimilar prescribing policy' administrative note encouraging the use of biosimilar brands for treatment naïve patients (this note will need to be updated for the other biosimilar brands of adalimumab to include Ardalicip in the list):
Prescribing of the biosimilar brand, Amgevita, Ardalicip, Hadlima, Hyrimoz, Idacio or Yuflyma is encouraged for treatment naïve patients.
Encouraging biosimilar prescribing for treatment naïve patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Medicines webpage (www.health.gov.au/health-topics/medicines)
- 6.6 The PBAC advised that, under Section 101(4AACD) of the Act, in the Schedule of Pharmaceutical Benefits:
- Humira and Ardalicip PFS should be treated as equivalent to each other; and Humira and Ardalicip PFP should be treated as equivalent to each other for the purposes of substitution (i.e. 'a' flagged in the Schedule).
 - 40 mg in 0.4 mL Ardalicip PFS and 40 mg in 0.8 mL Amgevita, Hadlima, Hyrimoz and Idacio PFS should be treated as equivalent to each other for the purpose of substitution (i.e. 'a' flagged in the Schedule).
 - 40 mg in 0.4 mL Ardalicip PFP and 40 mg in 0.8 mL Amgevita, Hadlima, Hyrimoz and Idacio PFP should be treated as equivalent to each other for the purpose of substitution (i.e. 'a' flagged in the Schedule).
- 6.7 The PBAC advised that, under Section 101(4AACD) of the Act, in the Schedule of Pharmaceutical Benefits, Ardalicip PFP should not be considered equivalent for the purposes of substitution with any adalimumab PFS, consistent with its previous considerations of adalimumab.
- 6.8 The PBAC agreed that Ardalicip will likely substitute for existing adalimumab brands and therefore not increase overall market utilisation.
- 6.9 The PBAC noted that its recommendation was on a cost-minimisation basis and

advised that, because Ardalicip is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over Humira, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

6.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new adalimumab brand (Ardalicip) with schedule equivalence ('a' flag) for the same indications as Humira as noted in Section 3.

7.2 Amend existing/recommended listing as follows:

- Authority Required listing of Ardalicip, with the Authority type for each treatment phase and indication to be consistent with current listings for the other biosimilar brands of adalimumab.
- The application of the 'Biosimilar prescribing policy' administrative note encouraging the use of biosimilar brands for treatment naïve patients (this note will need to be updated for the other biosimilar brands of adalimumab to include Ardalicip in the list):

Prescribing of the biosimilar brand Amgevita, Ardalicip, Hadlima, Hyrimoz, Idacio or Yuflyma is encouraged for treatment naïve patients.

Encouraging biosimilar prescribing for treatment naïve patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the B Medicines webpage (www.health.gov.au/health-topics/medicines)

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

8 Context for Decision

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

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

9 Sponsor's Comment

The sponsor had no comment.