Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Ardalicip / Ciptunec

Active ingredient: adalimumab

Sponsor: Cipla Australia Pty Ltd

April 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The 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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ASA	Australia specific annex
AU	Australia
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time zero to last measurable concentration
CI	Confidence interval
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CV	Coefficient of variation
DLP	Data lock point
DMARD	Disease modifying anti-rheumatic drug
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
PASI	Psoriasis Area and Severity Index
PI	Product Information
RMP	Risk management plan
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time to reach maximum concentration
TNF	Tumour necrosis factor
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	New biosimilar entity
Product names:	Ardalicip/Ciptunec
Active ingredient:	Adalimumab
Decision:	Approved
Date of decision:	23 August 2022
Date of entry onto ARTG:	6 September 2022
ARTG numbers:	373065, 374373, 374374, 374375, 374376 and 374377
, *Black Triangle Scheme:*	No
Sponsor's name and address:	Cipla Australia Pty Ltd Level 1/132-136 Albert Road, South Melbourne VIC 3205.
Dose form:	Solution for subcutaneous injection
Strengths:	40 mg/0.4 mL and 80 mg/0.8 mL
Containers:	Pre-filled syringe and pre-filled pen
Pack sizes:	40 mg/0.4 mL :1, 2 and 6 pre-filled syringes and pre-filled pen 80 mg/0.8 mL: 1 pre-filled syringe
Approved therapeutic use:	***Rheumatoid arthritis*** *Ciptunec and Ardalicip are indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.* *Ciptunec and Ardalicip can be used alone or in combination with methotrexate.* ***Juvenile idiopathic arthritis*** ***Polyarticular juvenile idiopathic arthritis*** *Ciptunec and Ardalicip in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older weighing ≥ 30 kg who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Ciptunec and Ardalicip can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.*

Enthesitis-related arthritis

Ciptunec and Ardalicip are indicated for the treatment of enthesitis-related arthritis in children, who have had an inadequate response to, or who are intolerant to, conventional therapy.

Psoriatic arthritis

Ciptunec and Ardalicip are indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing spondylitis

Ciptunec and Ardalicip are indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's disease in adults and children (≥ 6 years; weighing ≥ 40 kg)

Ciptunec and Ardalicip are indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients;

- *who have had an inadequate response to conventional therapies or,*
- *who have lost response to or are intolerant to infliximab*

Ulcerative colitis

Ciptunec and Ardalicip are indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see section 5.1 Pharmacodynamic properties -clinical trials).

Psoriasis in adults and children

Ciptunec and Ardalicip are indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Ciptunec and Ardalicip are indicated for the treatment of severe chronic plaque psoriasis in children and adolescent patients from 4 years of age weighing ≥ 40 kg who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

	Hidradenitis suppurativa in adults and adolescents (from 12 years of age)
	Ciptunec and Ardalicip are indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in patients with an inadequate response to conventional systemic hidradenitis suppurativa therapy.
	Uveitis
	Ciptunec and Ardalicip are indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.
Route of administration:	Subcutaneous injection
Dosage:	Ardalicip and Ciptunec (adalimumab) are biosimilar medicines to Humira. The comparability of Ardalicip and Ciptunec with Humira has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes (see Section 5 Pharmacological Properties, 5.1 Pharmacodynamic properties, Clinical trials and 4.8 Adverse Effects of the Product Information). The evidence for comparability supports the use of Ardalicip or Ciptunec for the listed indications. Ardalicip and Ciptunec are administered by subcutaneous injection. This product is for one dose in one patient only. Patients treated with Ardalicip or Ciptunec should be given the patient reminder card. Healthcare providers should be advised that there is no dosage form of Ardalicip or Ciptunec available which allows dosing of less than 40 mg. As a result, there are no suitable Ardalicip dosage forms available for a subset of the paediatric indications for this drug. The recommended dosage for Ciptunec and Ardalicip depends on the condition, age and weight of the patient. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	C 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 submission by Cipla Australia Pty Ltd (the sponsor) to register Ardalicip (adalimumab) and Ciptunec (adalimumab) 40 mg/0.4 mL and 80 mg/0.8 mL, solution for subcutaneous injection for the following proposed indication:

Rheumatoid arthritis

Ardalicip/Ciptunec is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Ardalicip/Ciptunec can be used alone or in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Ardalicip/Ciptunec in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Ardalicip/Ciptunec can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-related arthritis

Ardalicip/Ciptunec is indicated for the treatment of enthesitis-related arthritis in children, who have had an inadequate response to, or who are intolerant to, conventional therapy.

Psoriatic arthritis

Ardalicip/Ciptunec is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing spondylitis

Ardalicip/Ciptunec is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Psoriasis in adults and children

Ardalicip/Ciptunec is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Ardalicip/Ciptunec is indicated for the treatment of severe chronic plaque psoriasis in children and adolescent patients from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Hidradenitis suppurativa in adults and adolescents (from 12 years of age)

Ardalicip/Ciptunec is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in patients with an inadequate response to conventional systemic hidradenitis suppurativa therapy.

Uveitis

Ardalicip/Ciptunec is indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.

Adalimumab is a recombinant human immunoglobulin monoclonal antibody that selectively binds to tumour necrosis factor (TNF)-alpha and blocks it interaction with the cell surface TNF receptors resulting in a neutralisation of TNF effects in inflammatory conditions.

With this submission the sponsor proposes to register two adalimumab-containing medicines (Ardalicip and Ciptunec), as biosimilar versions of Humira (adalimumab), a biological medicine already registered in Australia. Humira is known as the reference product for this submission.[1]

The innovator adalimumab product (Humira, AbbVie Pty Ltd) was first registered in Australia in 2003, for the treatment of rheumatoid arthritis. Humira has since had extensions of indication approved for juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis.To date, seven adalimumab biosimilars have been registered in Australia: Amgevita,[2] Hadlima,[3] Hyrimoz,[4] Idacio,[5] Abrilada;[6] Hulio;[7] and Yuflyma.[8]

In addition, several other TNF inhibitors have been registered in Australia for one or more of the chronic inflammatory conditions. These include infliximab,[9] etanercept,[10] adalimumab, golimumab;[11] and certolizumab pegol.[12]

Regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

At the time the TGA considered this submission, similar submissions had been received marketing authorisation by the European Union (EU) centralised procedure on 12 November 2021 and by the United Kingdom on 5 January 2022 and Canada on 17 January 2022.

The following table summarises these submissions and provides the indications where approved.

[1] A **biosimilar medicine** is a version of an already registered biological medicine (known as the reference medicine). Both the biosimilar and its reference medicine will have similar characteristics (demonstrated using comprehensive comparability studies) for physicochemical, biological, and immunological properties, and clinical efficacy and safety. Most biosimilar medicines are likely to contain biotechnology-derived proteins as the active substance(s), but biosimilar medicines may include vaccines, and polysaccharides, such as low molecular weight heparins. Further information on biosimilar medicines is available on the TGA website: Biosimilar medicines regulation | Therapeutic Goods Administration (TGA).

[2] Amgevita was first registered in Australia on 9 November 2017. ARTG number: 278701.

[3] Hadlima was first registered in Australia on 24 August 2018. ARTG number: 284248.

[4] Hyrimoz was first registered in Australia on 1 March 2019. ARTG number: 291937.

[5] Idacio was first registered in Australia on 17 June 2020. ARTG number: 320241.

[6] Abrilada was first registered in Australia on 22 February 2021. ARTG number: 334496.

[7] Hulio was first registered in Australia on 14 May 2021. ARTG number: 334800.

[8] Yuflyma was first registered in Australia on 25 March 2022. ARTG numbers: 358350, 367770 and 367771.

[9] Infliximab was first registered in Australia on 2 August 2000. ARTG number: 73827.

[10] Etanercept was first registered in Australia on 18 March 2003. ARTG number: 90456.

[11] Golimumab was first registered in Australia on 13 November 2009. ARTG number: 153181.

[12] Certolizumab pegol was first registered in Australia on 20 January 2010. ARTG number: 154726.

Table 1: International regulatory status

Region	Status	Approved indications for
European Union	Approved on 12 November 2021	Rheumatoid arthritis Juvenile idiopathic arthritis Axial spondyloarthritis Psoriatic arthritis Psoriasis Paediatric plaque psoriasis Hidradenitis suppurativa Crohn's disease Paediatric Crohn's disease Ulcerative colitis Paediatric ulcerative colitis Uveitis Paediatric uveitis
Canada	Approved on 5 January 2022	Rheumatoid Arthritis Polyarticular Juvenile Idiopathic Arthritis Psoriatic Arthritis Ankylosing Spondylitis Adult Crohn's Disease Adult Ulcerative Colitis Hidradenitis Suppurativa Plaque Psoriasis Adult Uveitis Pediatric Uveitis Polyarticular JIA Adolescent Hidradenitis Suppurativa Pediatric Uveitis

Region	Status	Approved indications for
United Kingdom	Approved on 17 January 2022	Rheumatoid arthritis Juvenile idiopathic arthritis Axial spondyloarthritis Psoriatic arthritis Psoriasis Paediatric plaque psoriasis Hidradenitis suppurativa Crohn's disease Paediatric Crohn's disease Ulcerative colitis Paediatric ulcerative colitis Uveitis Paediatric uveitis

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 PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2021-02447-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2021
First round evaluation completed	15 March 2022
Sponsor provides responses on questions raised in first round evaluation	6 May 2022
Second round evaluation completed	19 August 2022
Delegate's Overall benefit-risk assessment	29 July 2022
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	23 August 2022
Completion of administrative activities and registration on the ARTG	6 September 2022

Description	Date
Number of working days from submission dossier acceptance to registration decision*	147

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines referred to by the Delegate or relevant to the submission are listed below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1.

  TGA-adopted; effective 25 May 2015

- European Medicines Agency (EMA): Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98.

  TGA-adopted; 16 June 2011

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. CHMP/EWP/89249/2004.

  TGA-adopted; effective 6 January 2009

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-clinical and Clinical Issues, EMA/CHMP/BMWP/403543/2010.

  TGA-adopted; effective 17 August 2015.

- European Medicines Agency (EMA), Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 corr

  TGA-adopted; effective 28 July 2005.

Quality

Ardalicip/Ciptunec;[13] is a clear, colourless, sterile, preservative free solution for subcutaneous injection containing:

- 40 mg of adalimumab in 0.4 mL solution (AVT02-DP40)
- 80 mg of adalimumab in 0.8 mL solution (AVT02-DP80)

To support the quality profile of the product, a comparability study was performed to characterise batches of Ardalicip/Ciptunec (that is, the sponsor's adalimumab-containing product), European Union (EU)-sourced Humira and US-sourced Humira. A comparability bridging assessment based on analytical results from EU-sourced Humira versus Australia-sourced (AU)-Humira is also presented. Three batches of AU-sourced Humira, three batches of

[13] AVT02 is sponsor development code for Ardalicip/Ciptunec.

EU-sourced Humira and three batches of Ardalicip/Ciptunec were tested to confirm chemical and physical similarity (see Table 3 and Table 4).

Table 3: Assessment between the Ardalicip/Ciptunec and its two reference products

	Ardalicip/Ciptunec	EU-Humira	US-Humira
Ardalicip/Ciptunec	Characterisation study	Multiple batches of comparative analytical similarity assessments	
AU-Humira	Three batches of bridging comparability assessment for each product		

Table 4: Biosimilarity, comparability and bridging study assessment

	Ardalicip/Ciptunec	EU-Humira	US-Humira
Ardalicip/Ciptunec		Comparative analytical similarity assessments	
		Comparable	**Comparable**
EU-Humira			**Highly comparable**
AU-Humira	Bridging comparability assessment		
	Comparable	**Highly Comparable**	

Regarding requirements for reference medicines the TGA Biosimilar medicines guidance states:

> 'If sponsor is using a reference medicine for the comparability studies that has not been registered in Australia, sponsor must meet the following requirements:
>
> - the reference medicine must be approved for general marketing by a regulatory authority with similar scientific and regulatory standards as TGA (for example, European Medicines Agency (EMA) or United States Food and Drug Administration (FDA))
> - a bridging study must be provided to demonstrate that the comparability studies are relevant to the Australian reference medicine (this bridging study may be abridged or omitted if you include evidence that the medicine is manufactured in a single site for global distribution)'

This requirement aligns with the TGA adopted CHMP Guideline on Similar Biological Medicinal Products.[14] Studies showed that:

- total afucosylation of Ardalicip/Ciptunec was slightly lower and afucosylation without high mannose was slightly higher compared to Humira;
- levels of high mannose in Ardalicip/Ciptunec were lower than in Humira; and
- slightly higher levels of sialylated glycans were observed in Ardalicip/Ciptunec.

Based on the overall (physicochemical and biological) comparability assessment and substantial overlap in the glycosylation fingerprint between Ardalicip/Ciptunec and the reference product Humira, the TGA's quality evaluation concluded that Ardalicip/Ciptunec satisfied the requirements for biosimilarity with the reference product. The quality evaluation considered that Ardalicip/Ciptunec should also display similar clinical efficacy and safety, including immunogenicity, to the reference product to confirm biosimilarity.

[14] CHMP/437/04 Rev. 1 Guideline on similar biological medicinal products

Recommend wording for quality related conditions of registration

The quality evaluator recommended the following proposed conditions of registration:

- Laboratory testing & compliance with Certified Product Details (CPD)

1. All batches of Ciptunec and Ardalicip (adalimumab) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

2. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Nonclinical

The nonclinical dossier contained one comparative study investigating pharmacokinetics and local tolerance (assessment of erythema and oedema) in cynomolgus monkeys. This study was conducted using EU-sourced Humira as the reference product. No data were provided in nonclinical dossier to verify the comparability of the EU-sourced and Australia-sourced Humira.

Comparable serum kinetic profiles after subcutaneous administration were observed for Ardalicip/Ciptunec and EU-sourced Humira in the monkey study. Local tolerance investigations in this study, although limited, indicated good local tolerability of the Ardalicip/Ciptunec product that was comparable to EU-sourced Humira.

The ability of the nonclinical studies to support comparability to Australian-sourced Humira depends on the conclusion of the quality evaluator regarding: (i) the ability of the *in vitro* pharmacology studies and the comparative analytical similarity assessment to support the biosimilarity of Ardalicip/Ciptunec and EU-sourced Humira, and (ii) the identity of Humira products across jurisdictions. Provided these conditions are met, there are no nonclinical objections to the registration of Ardalicip/Ciptunec.

The nonclinical evaluation recommended that the sponsor include a subsection in 'Section 5.1 Pharmacological Properties' of the Product Information (PI), which outlines the assessments that showed comparable in vitro biological actions and binding of the biosimilar relative to the innovator Humira.

There are no nonclinical objections to the registration of Ardalicip/Ciptunec.

Clinical

Summary of clinical studies

The TGA's clinical evaluation recommended approval of all three presentations of the biosimilar adalimumab for injection for the same indications approved for the innovator in rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, Crohn's disease in adults and children (aged 6 years and older, weighing 40 kg or more), psoriasis, ulcerative colitis in adults and children, hidradenitis suppurativa in adults and adolescents, and uveitis.

The clinical evaluation noted that in the absence of a 20 mg formulation, Ardalicip/Ciptunec would not be suitable for smaller paediatric patients. The clinical recommendation was subject to the quality evaluation concluding that the quality, and comparability of the reference product Humira with Ardalicip/Ciptunec were acceptable.

The clinical dossier consisted of:

- Two Phase I studies:
  - Study AVT02-GL-101: A Phase I pharmacokinetic study assessing the bioequivalence between EU-Humira, US-Humira and Ardalicip/Ciptunec in healthy volunteers.
  - Study AVT02-GL-102: A Phase I study assessing the bioequivalence between Ardalicip/Ciptunec-pre-filled syringe and Ardalicip/Ciptunec-autoinjector in healthy volunteers.
- Two Phase III studies:
  - Study AVT02-GL-301: A Phase III therapeutic equivalence study between Ardalicip/Ciptunec and EU-Humira in adults with psoriatic arthritis.
  - Study AVT02-GL-303: A Phase III study assessing the handling experience with an autoinjector in patients with rheumatoid arthritis.
- One pharmacokinetic study:
  - Study AVT02-GL-100: A first in human pharmacokinetic study of Ardalicip/Ciptunec compared to EU-Humira. This study assessed Ardalicip/Ciptunec manufactured using an earlier process than that presented for the commercial product.
- One report from human factor study:
  - Study ACT (with AVT02 HF validation autoinjector): This study explores the usability of the autoinjector device by the intended users was also provided.

Pharmacology

Pharmacokinetics

In Study AVT02-GL-101, the systemic absorption of adalimumab following a single 40 mg subcutaneous dose in healthy volunteers was slow with median time to reach maximum concentration (T_{max}) of 192 hours in the Ardalicip/Ciptunec and US-sourced Humira groups and 168 hours in the EU-Humira group. The geometric coefficient of variation (CV)% for T_{max} was moderate at 45 to 48%. The 90% confidence interval (CI) for the geometric mean values for the three primary pharmacokinetic endpoints maximum concentration (C_{max}), area under the concentration time curve from time zero to last measurable concentration (AUC_{0-t}) and area under the concentration-time curve from time zero to infinity (AUC_{0-inf}), were contained within

the respective bioequivalence margins of 80% to 125% in pairwise comparisons of Ardalicip/Ciptunec, EU-Humira and US-Humira. The CV% for serum adalimumab concentrations were moderately large, greater or equal to 50% to 48 hours post dose, 30 to 50% to Day 22 and greater than 100% from Day 50. The clearance of adalimumab was slow with a geometric mean clearance of 18 to 20 mL/h; the terminal half-life ranged from 160 to 174 hours. The results were consistent across the three treatment groups. The CV% for these parameters was similarly high (greater than 50%) across all treatment groups.

In Study AVT02-GL-102, the absorption of adalimumab following a 40 mg subcutaneous dose (using either a prefilled syringe or autoinjector) to healthy volunteers was also slow. The T_{max} was 168 hours. The geometric mean pharmacokinetic parameters for the pre-filled syringe and autoinjector groups were comparable. The 90% CIs for the geometric mean values of C_{max}, AUC_{0-t} and AUC_{0-inf} were contained within the respective bioequivalence margins of 80% to 125% for the three pairwise comparisons. The CV% for serum adalimumab concentrations were moderately large but consistent. Systemic exposure (C_{max} and area under the concentration time curve (AUC)) was higher in participants in the lower body weight category (50 to 81.9 kg) and decreased with increased weight. Clearance increased with increasing weight group while the half-life did not show any trend. This phenomenon has previously been noted with adalimumab.

In Study AVT02-GL-301, a Phase III, randomised, controlled clinical equivalence study in adults with moderate to severe psoriasis, 205 participants who received Ardalicip/Ciptunec and 207 participants who received EU-sourced Humira contributed pharmacokinetic data. Trough concentrations (C_{trough}) of adalimumab in serum were determined using the same validated assay as in Study AVT02-GL-101. Mean C_{trough} were slightly higher in the Ardalicip/Ciptunec than the EU-sourced Humira groups throughout the study. The difference was not statistically tested.

Anti-drug antibody positivity and neutralising antibody positivity was very common and comparable in all studies using Ardalicip/Ciptunec, EU-Humira and US-Humira. In all the three groups anti-drug antibody positivity was greater than 90% and neutralising antibody positivity was greater than 80%.

Efficacy

There was one Phase III clinical efficacy study (Study AVT02-GL-301) conducted in patients with chronic psoriasis, which assessed the therapeutic equivalence of Ardalicip/Ciptunec to EU-sourced Humira.

Study AVT02-GL-301 was a multicentre, double blind, randomised, parallel group, active control study comparing the efficacy, safety, and immunogenicity in patients with moderate to severe plaque psoriasis.

The primary objective was to compare the Psoriasis Area and Severity Index (PASI);[15] response to Ardalicip/Ciptunec and EU-sourced Humira at Week 16. Participants with an adequate response at Week 16 continued on study for up to 58 weeks.

The study included adults 18 to 75 years of age with stable, moderate to severe, chronic plaque psoriasis for at least two months who had a previous failure, inadequate response, intolerance, or contraindication to at least one systemic anti-psoriatic therapy. Exclusion criteria were

[15] Psoriasis Area and Severity Index (PASI): Total PASI scores were calculated by multiplying the area of involvement score, the sum of the severity scores for erythema, induration, and scaling, and a weight factor for that body area (0.1, 0.2, 0.3, and 0.4 for head, upper extremities, trunk, and lower extremities, respectively), and then summing across all 4 body areas. The total range of the PASI score is 0 to 72, where 0 = no psoriasis and 72 = severe disease.
The PASI 50 response indicates a 50% or more reduction (improvement) in PASI score from Baseline.
The PASI 75 response indicates a 75% or more reduction (improvement) in PASI score from Baseline.
The PASI 90 response indicates a 90% or more reduction (improvement) in PASI score from Baseline.

comprehensive and included prior use of two or more biologics to treat psoriasis; other types of psoriasis or other skin conditions or systemic autoimmune inflammatory disease; topical psoriasis medications within two weeks; phototherapy within four weeks; and other, nonbiologic, systemic therapy for psoriasis within four weeks.

Participants received a loading dose of 80 mg subcutaneous (2 x 40 mg syringes) of Ardalicip/Ciptunec or EU-sourced Humira followed by 40 mg subcutaneous once every other week, starting one week after the loading dose, until Week 14.

At Week 16, non-responding participants (less than 50% improvement in PASI) were withdrawn from the study and responding subjects (at least PASI 50) began Stage 2 (long term efficacy and safety assessment) of the active period. For responders entering Stage 2, those on Ardalicip/Ciptunec continued on Ardalicip/Ciptunec and those on EU-sourced Humira were re-randomised to Group 2A and received Ardalicip/Ciptunec or Group 2B to receive EU-sourced Humira. All dosing was 40 mg subcutaneous once every other week.

The primary efficacy endpoint was the percent improvement in PASI from Baseline to Week 16; several secondary and exploratory endpoints were also included in the protocol. An analysis of covariance model was used to assess the efficacy of Ardalicip/Ciptunec compared to Humira at Week 16 with presence or absence of psoriatic arthritis and prior use of biological therapy for the treatment of psoriasis or psoriatic arthritis as factors and baseline PASI score as a covariate. Equivalence between treatments was assumed if the two sided 90% CI (for the FDA guideline) and 95% CI (for the EMA guideline) lay within the range of -10% to 10%.[16]

Demographic and baseline disease characteristics in the treatment groups were comparable.

The least square mean change from baseline to Week 16 in the PASI (applying a last observation carried forward imputation strategy) was 89.2% and 86.9% in the Ardalicip/Ciptunec and EU-Humira groups, respectively. The least square mean difference was 2.3 (95% CI: -1.34, 5.88). As this 95% CI was contained within the predefined bioequivalence margin of plus/minus 10% the study was considered positive. The bioequivalence margin required by the FDA was also achieved.

Sensitivity analyses including a mixed model for repeated measure on the full analysis set were consistent with the primary analysis. Results for secondary outcomes and exploratory outcomes were also supportive. Comparable clinical improvement was maintained to 50 weeks. Most participants developed anti-drug antibody positivity during the study and anti-drug antibody titres were similar between groups over the duration of the study.

Safety

The clinical development program for Ardalicip/Ciptunec exposed 743 adults to Ardalicip/Ciptunec including 107 with rheumatoid arthritis, 302 with psoriasis and 334 healthy volunteers. Studies were designed to have direct comparison with the EU-Humira and in one healthy volunteer pharmacokinetic study there was a third arm with US-Humira.

Study AVT02-GL-301 was the primary source of comparative clinical safety data for Ardalicip/Ciptunec. Safety parameters included treatment emergent adverse events (TEAEs), injection site reactions via direct assessment and diary recording, clinical laboratory parameters (chemistry, haematology and urinalysis), immunogenicity, monitoring for tuberculosis, vital signs, 12-lead electrocardiogram, chest X-ray and physical examination.

[16] European Medicines Agency (EMA), Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 corr

The safety analysis set was reported for all participants who received at least one dose of study drug with treatment assignment based on actual treatment received. TEAEs of special interest included infections, malignancies, hypersensitivity, demyelinating diseases, haematologic reactions, heart failure, lupus like syndromes, liver enzyme elevations, injection site reactions and anaphylactic reactions.

The rate of TEAEs was comparable between Ardalicip/Ciptunec and EU-sourced Humira and comparability extended to the severity assessment and adverse event profile. Although adverse events were relatively frequent (44.9% Ardalicip/Ciptunec versus 44% Humira to Week 16), they were generally mild or moderate in severity and the rate of severe TEAEs was low (2% versus 1.4% to Week 16 in the psoriasis study). The most common events were injection site reactions and rates were comparable between Ardalicip/Ciptunec and Humira (16.6% versus 15.9%). These were the most common treatment related adverse events. Infections were the most notable TEAEs of special interest as would be expected with this product.

Analysis of safety in patients with psoriatic arthritis did not reveal any signals nor were there any new safety signals from the healthy volunteer single dose studies where AE rates were comparable between Ardalicip/Ciptunec, EU-sourced Humira and US-sourced Humira. There was also comparable safety demonstrated between the Ardalicip/Ciptunec delivered via a pre-filled syringe and an autoinjector.

Device/drug delivery

Usability studies for the autoinjector device were presented with this submission. Usability was considered appropriate, however training in use of the device is recommended before use.

Risk management plan

Cipla Australia Pty Ltd has submitted EU-risk management plan (RMP) version 0.3 (30 July 2021; data lock point (DLP) 12 March 2020) and Australia specific annex (ASA) version 1.0 (9 August 2021) in support of this application. At second round of evaluation, no updated EU-RMP or ASA was provided with the sponsor's response. At third round of evaluation, the sponsor has submitted ASA version 1.1 (05 July 2022) in association with previously submitted EU-RMP version 0.3 (30 July 2021; DLP 12 March 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Serious infections	ü	-	ü	ü*
	Tuberculosis (TB)	ü	-	ü	ü*
	Malignancies	ü	-	ü	ü*
	Demyelinating disorders (including multiple sclerosis (MS), Guillain Barré syndrome (GBS) and optic neuritis)	ü	-	ü	ü*
	Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with in utero exposure to adalimumab	ü	-	ü	ü*
Important potential risks	Progressive Multifocal Leukoencephalopathy (PML)	ü	-	-	-
	Reversible posterior leukoencephalopathy syndrome (RPLS)	ü	-	-	-
	Adenocarcinoma of colon in ulcerative colitis (UC) patients	ü	-	-	-
Missing information	Patients with Immune Compromised conditions	ü	-	ü	-
	Episodic treatment in Ps, UC and JIA	ü	-	-	-
	Long-term safety information in the treatment of children with uveitis	ü	-	ü	-
	Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis.	ü	-	-	-
	Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	ü	-	-	-

* Patient reminder card

The important identified and potential risks in the summary of safety concerns align with the current Humira reference product RMP and those listed in the supplied EU-RMP in support of Ciptunec/Ardalicip. The summary of safety concerns is acceptable from an RMP perspective.

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted for the proposed products. Furthermore, no additional pharmacovigilance activities have been proposed. This aligns with the EU-RMP, however, Humira treatment is included in a number of international registries which monitor serious infection, tuberculosis and malignancies as events of special interest. From an RMP perspective, though biosimilar sponsors are strongly encouraged to participate in international registries where follow up of adalimumab is ongoing this is generally not a regulatory requirement. From an RMP perspective, the proposed plan is acceptable.

The proposed risk minimisation plan aligns with the reference product RMP and supplied biosimilar EU-RMP. Routine and additional risk minimisation activities are proposed for all identified risks. Routine risk minimisation is also proposed for missing information relating to 'Patients with immune compromised conditions' and 'Long-term safety information in the treatment of children with uveitis'. Additional risk minimisation activity proposed for the important identified risks are in the form of adult and paediatric patient reminder cards. The sponsor commits to submitting mock-ups of the adult and paediatric patient reminder cards and details of the card's distribution plan, to TGA for review and approval, prior to product launch which is an acceptable approach. The risk minimisation plan is acceptable from an RMP perspective.

Recommended wording for risk management plan related conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> 'The adalimumab EU-RMP (version 0.3, dated 30 July 2021, data lock point 12 March 2020), with ASA (version 1.1, dated 5 July 2022), included with submission PM-2021-02447-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.'

Risk-benefit analysis

Delegate's considerations and proposed action

The sponsor has provided sufficient evidence of physicochemical, biological and clinical comparability to the reference product Humira to allow registration as a biosimilar medicine in Australia. The absence of suitable paediatric formulations for smaller and younger patients has been addressed in the PI.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Ardalicip/Ciptunec (adalimumab) 40 mg/0.4 mL and 80 mg/0.8 mL, solution for subcutaneous injection, pre-filled syringe, pre-filled pen, indicated for:

Rheumatoid arthritis

Ciptunec and Ardalicip are indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Ciptunec and Ardalicip can be used alone or in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Ciptunec and Ardalicip in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older weighing ≥ 30 kg who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Ciptunec and Ardalicip can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-related arthritis

Ciptunec and Ardalicip are indicated for the treatment of enthesitis-related arthritis in children, who have had an inadequate response to, or who are intolerant to, conventional therapy.

Psoriatic arthritis

Ciptunec and Ardalicip are indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing spondylitis

Ciptunec and Ardalicip are indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's disease in adults and children (≥ 6 years; weighing ≥ 40 kg)

Ciptunec and Ardalicip are indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients;

- *who have had an inadequate response to conventional therapies or,*
- *who have lost response to or are intolerant to infliximab*

Ulcerative colitis

Ciptunec and Ardalicip are indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see section 5.1 Pharmacodynamic properties -clinical trials).

Psoriasis in adults and children

Ciptunec and Ardalicip are indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Ciptunec and Ardalicip are indicated for the treatment of severe chronic plaque psoriasis in children and adolescent patients from 4 years of age weighing ≥ 40 kg who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Hidradenitis suppurativa in adults and adolescents (from 12 years of age)

Ciptunec and Ardalicip are indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in patients with an inadequate response to conventional systemic hidradenitis suppurativa therapy.

Uveitis

Ciptunec and Ardalicip are indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.

Specific conditions of registration applying to these goods

- The adalimumab EU-RMP (version 0.3, dated 30 July 2021, DLP 12 March 2020), with ASA (version 1.1, dated 5 July 2022), included with submission PM-2021-02447-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration

- Laboratory testing & compliance with Certified Product Details (CPD)

  a. All batches of Ciptunec and Ardalicip (adalimumab) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  b. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

  Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The PI for Ardalicip approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

The PI for Ciptunec is identical except for the product name.

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Reference/Publication #