



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Adalimumab

Proprietary Product Name: Hulio

Sponsor: Alphapharm Pty Ltd

November 2021

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACR20	American College of Rheumatology 20% (improvement) response
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
AUC _{0-360h}	Area under the curve from time zero to 360 hours
AUC _{0-∞}	Area under the curve from time zero to infinity
AUC _{0-t}	Area under the curve from time zero to last measurable concentration
bDMARD	Biological disease modifying anti-rheumatic drug
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C _{max}	Maximum concentration
CPD	Certified Product Details
CRP	C-reactive protein
DAS	Disease Activity Score
DLP	Data lock point
DMARD	Disease modifying anti-rheumatic drug
EMA	European Medicines Agency (European Union)
ESR	Erythrocyte sedimentation rate
EU	European Union

Abbreviation	Meaning
FDA	Food and Drug Administration (United States of America)
FKB327	Sponsor's drug development code for Hulio (adalimumab)
GVP	Good Pharmacovigilance Practices
LSM	Least square means
nAb	Neutralising antibody
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
RMP	Risk management plan
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
TNF α	Tumour necrosis factor alpha
US(A)	United States (of America)

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biosimilar medicine
<i>Product name:</i>	Hulio
<i>Active ingredient:</i>	Adalimumab
<i>Decision:</i>	Approved
<i>Date of decision:</i>	7 April 2021
<i>Date of entry onto ARTG:</i>	14 May 2021
<i>ARTG number:</i>	334800, 334801, 334802
<i>▼ Black Triangle Scheme:¹</i>	No
<i>Sponsor's name and address:</i>	Alphapharm Pty Ltd Level 1, 30 The Bond, 30 to 34 Hickson Road, Millers Point, NSW 2000
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	20 mg/0.4 mL and 40 mg/0.8 mL
<i>Containers:</i>	Pre-filled syringe (0.4 mL sterile solution) Pre-filled syringe and pre-filled pen (0.8 mL sterile solution)
<i>Pack sizes:</i>	2 pre-filled syringes (0.4 mL sterile solution) 1, 2 and 6 pre-filled syringes or pre-filled pens (0.8 mL sterile solution)
<i>Approved therapeutic use:</i>	<i>Rheumatoid arthritis</i> <i>Hulio 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.</i> <i>Hulio can be used alone or in combination with methotrexate.</i> <i>Juvenile idiopathic arthritis</i>

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

Polyarticular Juvenile Idiopathic Arthritis

Hulio 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 antirheumatic drugs (DMARDs). Hulio can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-related arthritis

Hulio 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

Hulio 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

Hulio is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's Disease in Adults and Children (≥ 6 years)

Hulio is 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

Hulio is 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 5.1 Pharmacodynamic Properties -Clinical Trials).

Psoriasis in adults and children

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

Hulio 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)

Hulio 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

Hulio 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.

Route of administration: Subcutaneous injection

Dosage: Dosage of Hulio is based on multiple factors, including the condition being treated, the age and the body weight of the patient.

For further information 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 application by Alphapharma Pty Ltd (the sponsor) to register Hulio (adalimumab) 20 mg/0.4 mL and 40 mg/0.8 mL, solution for injection for the following proposed indication:

Rheumatoid arthritis

Hulio 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. Hulio can be used alone or in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Hulio 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 antirheumatic drugs (DMARDs). Hulio can be given as

monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-related arthritis

Hulio 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

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

Ankylosing spondylitis

Hulio is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's disease in adults and children (≥ 6 years)

Hulio is 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 of infliximab.

Ulcerative colitis

Hulio is 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 Clinical Trials).

Psoriasis

Psoriasis in adults and 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

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

Uveitis

Hulio 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.

Plaque psoriasis

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

Adalimumab is a biological disease modifying anti-rheumatic drug (bDMARD) that targets the cytokine tumour necrosis factor-alpha (TNF α). Blocking the action of TNF α reduces the inflammation of rheumatoid arthritis and other inflammatory conditions.

The first adalimumab drug approved for use in Australia (that is, the innovator medicine)² was Humira (sponsor: Abbvie Pty Ltd);³ and was registered in 2003 for the treatment of rheumatoid arthritis, and subsequently a range of other inflammatory conditions including juvenile idiopathic arthritis, enthesitis-related arthritis in children, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis.

To date, the TGA has approved other biosimilar alternatives to the innovator in Australia: Hyrimoz (sponsor: Sandoz Pty Ltd);⁴ Hadlima (sponsor: Samsung Bioepis AU Pty Ltd);⁵ Idacio (sponsor: Fresenius Kabi Australia Pty Ltd);⁶ and Amgevita (sponsor: Amgen Australia Pty Ltd);⁷ and most recently Abrilada (sponsor: Pfizer Australia Pty Ltd).⁸

The sponsor seeks registration of Hulio (sponsor's drug development code: FKB327) for the same indications as have been approved for the reference medicine Humira (adalimumab);.

Regulatory status

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

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) (on 16 September 2018) and the United States of America (USA) (on 3 July 2020), Canada (on 23 July 2020) and Switzerland (on 13 May 2020).

In the EU, Hulio was approved for essentially the same conditions as requested in Australia. In the USA, Hulio does not appear to have been approved for enthesitis-related arthritis, hidradenitis suppurativa, uveitis or for Crohn's disease or ulcerative colitis in children.

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>>.

² An innovator reference medicine is the existing medicine already on the market that biosimilar medicines are developed to be similar to.

³ Humira was first registered on the ARTG on 28 August 2012 (ARTG numbers: 199410, 199411 and 199412).

⁴ Hyrimoz was first registered on the ARTG on 1 March 2019 (ARTG numbers: 291937 and 291938).

⁵ Hadlima was first registered on the ARTG on 24 January 2018 (ARTG numbers: 284248 and 284249).

⁶ Idacio was first registered on the ARTG on 17 June 2020 (ARTG numbers: 320241, 320242 and 320243).

⁷ Amgevita was first registered on the ARTG on 9 November 2017 (ARTG number: 273536).

⁸ Abrilada was first registered on the ARTG on 22 February 2021 (ARTG number: 334496, 334497, 334498 and 334499).

II. Registration timeline

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

Table 1: Timeline for Submission PM-2020-01807-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	2 June 2020
First round evaluation completed	2 November 2020
Sponsor provides responses on questions raised in first round evaluation	12 January 2021
Second round evaluation completed	16 February 2021
Delegate's Overall benefit-risk assessment	15 March 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	7 April 2021
Completion of administrative activities and registration on the ARTG	14 May 2021
Number of working days from submission dossier acceptance to registration decision*	172

*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.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev1, 23 October 2014.
- Australian Government, Department of Health, Therapeutic Goods Administration, Biosimilar medicines regulation, Version 2.2, April 2018. Available at: <https://www.tga.gov.au/publication/biosimilar-medicines-regulation>.
- EMA, CHMP, Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues, EMA/CHMP/BMWP/403543/2010, 30 May 2012.

Quality

The quality evaluator reported no outstanding issues following the second round of quality evaluation, and no objections on quality grounds to the approval of Hulio adalimumab for registration.

The critical evaluations for this submission were the assessment of a full bioanalytical report on the physicochemical and biological similarity of Hulio adalimumab (FKB327) and EU-approved and US-licensed innovator Humira adalimumab products, and two bridging studies to show comparability between Hulio adalimumab (FKB327), EU-approved Humira adalimumab and the Australian innovator product Humira (Australian-registered Humira adalimumab), and comparability between EU-approved and US-licensed Humira (see Table 2).

Regarding requirements for reference medicines, the TGA biosimilar medicines guidance;⁹ states:

If you are using a reference medicine for your comparability studies that has not been registered in Australia, you 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, EMA [European Drugs Agency] or US FDA [Food and Drug Administration])*
- *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 Committee on Medicinal Products for Human Use (CHMP) Guideline on Similar Biological Medicinal Products.¹⁰

⁹ Australian Government, Department of Health, Therapeutic Goods Administration, Biosimilar medicines regulation, Version 2.2, April 2018. Available at: <https://www.tga.gov.au/publication/biosimilar-medicines-regulation>.

¹⁰ European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev1, 23 October 2014.

Table 2: Biosimilarity, comparability and bridging study assessments

	Hulio adalimumab (FKB327)	EU-approved Humira adalimumab	US-licensed Humira adalimumab
Hulio adalimumab (FKB327)	Characterisation	Biosimilarity Assessment (Hulio (FKB327) versus EU-approved Humira) Comparable	Biosimilarity Assessment (Hulio (FKB327) versus US-licensed Humira) Comparable
EU-approved Humira adalimumab			Comparability Assessment (US- licensed Humira adalimumab versus EU-approved Humira adalimumab) Highly comparable
Australia sourced Humira adalimumab	Bridging study		

Table 3: Comparison of Humira adalimumab and Hulio adalimumab (FKB327) formulations

	Humira	FKB327 drug product (Hulio)
Active substance	Adalimumab	Adalimumab
Dosage form	50 mg/mL solution for injection	50 mg/mL solution for injection
Container content	0.8 mL	0.8 mL
Administration	Subcutaneous	Subcutaneous
Formulation – active substance	40 mg adalimumab	40 mg FKB327 (adalimumab)
Formulation - excipients	Sodium chloride, monobasic sodium phosphate dehydrate, sodium citrate, citric acid monohydrate, mannitol, Polysorbate 80, sodium hydrate (adjust pH 5.2), water for injection	Monosodium glutamate, sorbitol, methionine, Polysorbate 80, hydrochloric acid (adjust pH 5.2), water for injection

The evaluator concluded that as the results of the biosimilarity assessments between Hulio adalimumab (FKB327) against US-licensed Humira (adalimumab); and Hulio

adalimumab (FKB327) against EU-approved Humira (adalimumab) were identical, and Hulio (FKB327) may be considered comparable to both products. The comparability study between US-licensed and EU-approved Humira (adalimumab) indicated that both of those products were highly comparable, as were the Australian-registered and EU-approved Humira adalimumab in the additional comparability study.

The reports identified some minor physicochemical differences between Hulio adalimumab (FKB327) and the Humira adalimumab products that did not appear to affect the biological activity of the product. The evaluator agreed that these minor differences were unlikely to have clinical consequences.

The specific noted differences were:

- glycan composition and distribution of Hulio adalimumab (FKB327) differed from Australia-sourced Humira and EU-approved Humira adalimumab.
- glycosylation site occupancy % of Hulio adalimumab (FKB327) is higher than Australian-sourced Humira and EU-approved Humira adalimumab.
- methionine oxidation of all samples are similar in the light chain. Hulio adalimumab (FKB327) had slightly higher methionine 256 and 432 residues.
- compared with Australian-sourced Humira and EU-approved Humira adalimumab, the hydrophobic heterogeneity of the fragment crystallisable region of Hulio adalimumab (FKB327) for:
 - pre-peak was lower
 - main peak was higher
- acidic variant was higher for Hulio adalimumab (FKB327) and basic variant was lower for Hulio adalimumab (FKB327).
- the low molecular weight content (as a percentage) was slightly higher in Hulio adalimumab (FKB327).

Quality-related proposed conditions of registration

The following are quality-related proposed conditions of registration:

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

Nonclinical

The nonclinical evaluation concluded that there were no clinically meaningful differences observed between Hulio (adalimumab) and Humira (adalimumab) across the package of submitted comparative pharmacology, pharmacokinetic and toxicity studies. The scope of the submitted nonclinical dossier was in accordance with the relevant guideline.¹¹

The nonclinical dossier contained *in vivo* and *in vitro* comparative studies conducted using EU- or US-sourced Humira (adalimumab) as the reference product, and included pharmacology, pharmacokinetics and repeat-dose toxicity assessments. The *in vivo* comparative studies were all performed using EU-sourced Humira (adalimumab).

The nonclinical evaluator concluded that, provided that EU-sourced Humira (adalimumab) is considered to be identical or highly comparable to the Australian product, there are no nonclinical objections to the registration of Hulio (adalimumab).

The evaluator recommended that the PI, Section 5: Pharmacological Properties should be updated with a statement regarding the comparability of Hulio with Humira:

‘Comparability of Hulio with Humira

Pharmacodynamic comparability between Hulio and Humira was demonstrated *in vitro* as well as in an *in vivo* study using TNF α transgenic mice as a model of arthritis.

The *in vitro* assays assessed functional characteristics of innovator adalimumab (Humira) against biosimilar (Hulio). These demonstrated comparable binding with TNF α , Fc receptors (RI, RIIa, RIIb and FcRn) and C1q as well as comparable neutralisation of TNF- α cytotoxicity, apoptosis induction, antibody-dependent cellular cytotoxicity (ADCC), and complement-dependent cytotoxicity. While Hulio showed slightly higher affinities (lower K_D [equilibrium disassociation constant] values) than Humira for Fc γ RIII subtypes, (possibly due to higher levels of afucosylated complex type glycans in the former), this was not reflected in ADCC differences, and is not considered clinically significant.’

The sponsor included the recommended text with minor amendments (including references to Fc receptor types RIIa and RIIb demonstrating comparable binding between Hulio and Humira) under Section 5.1 Pharmacodynamic properties of the PI.

Clinical

Clinical evaluator’s recommendation regarding approval

The clinical evaluation recommended approval of all three presentations of Hulio (adalimumab) solution for injection. The recommendation for approval covered all indications approved for the reference product Humira (adalimumab), including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis with associated restrictions in the treatment population for each condition. The evaluator noted that the absence of an 80 mg formulation would require patients using higher dose regimens of adalimumab to use a minimum of two syringes per dose to achieve the regimen.

¹¹ EMA, CHMP, Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues, EMA/CHMP/BMWP/403543/2010, 30 May 2012.

The clinical recommendation was subject to the quality and nonclinical evaluators concluding that the quality and other nonclinical aspects of the biosimilarity assessment are acceptable.

Studies submitted

The clinical study reports included in this submission included:

- Study FKB327-005: a Phase I, randomised, open-label, single-dose study to assess the relative bioavailability of a subcutaneous dose of FKB327 (Hulio, adalimumab) when administered using either a pre-filled syringe, a pre-filled auto-injector or a vial with disposable syringe in healthy subjects
- Study FKB327-001: a randomised, double-blind, single-dose study to compare pharmacokinetic characteristics and safety of FKB327 (Hulio, adalimumab) with those of Humira (adalimumab) in healthy subjects.
- Study FKB327-002: a randomised, blinded, active-controlled study to compare FKB327 (Hulio, adalimumab) efficacy and safety with the comparator Humira (adalimumab) in rheumatoid arthritis patients inadequately controlled on methotrexate (note, this is also known as the ARABESC trial).
- Study FKB327-003: an open-label extension study to compare the long-term efficacy, safety, immunogenicity and pharmacokinetics of FKB327 (Hulio, adalimumab) and Humira (adalimumab) in patients with rheumatoid arthritis on concomitant methotrexate (an open-label extension to Study FKB427-003/ARABESC trial, interim clinical study report).
- Study FKB327-004: a Phase I, randomised, single-blind, single-dose study to compare pharmacokinetic characteristics and safety of FKB327 (Hulio, adalimumab) with those of Humira (adalimumab) in Japanese healthy subjects.

In addition, the sponsor submitted integrated summaries of safety, efficacy and pharmacokinetics comparing FKB327 (Hulio, adalimumab) and Humira (adalimumab) in adults with rheumatoid arthritis, an integrated summary of immunogenicity of FKB327 (Hulio, adalimumab) and supportive literature.

Pharmacology

Pharmacokinetics

Study FKB327-005 was a Phase I, randomised, open-label, parallel-group, single subcutaneous (SC) dose study the primary objective of which was to assess the relative bioavailability of FKB327 (Hulio, adalimumab) after a single SC dose delivered by vial/syringe (vial), prefilled syringe and autoinjector in healthy adults. This study did not compare the pharmacokinetics (PK) of FKB327 (Hulio, adalimumab) and Humira (adalimumab).

The 90% confidence intervals (CI) of the geometric least square means (LSM) means for comparisons of PK parameters between pre-filled syringe versus vial, autoinjector versus vial, and autoinjector versus pre-filled syringe were within the bioequivalence limits (0.8, 1.25) for the area under the curve from time zero to last measurable concentration (AUC_{0-t}), the area under the curve from time zero to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}) and terminal half-life ($t_{1/2}$), when adjusted for baseline anti-drug antibody (ADA) status.

Study FKB327-001, a first in human study of FKB327 (Hulio, adalimumab), was a Phase I, randomised, double-blind, parallel-group study that compared the safety and PK of

FKB327 (Hulio, adalimumab) and EU-approved and USA-licensed Humira (adalimumab) after single SC doses in healthy volunteers.

Analysis of covariance (ANCOVA) showed that the 90% CIs of the ratios of the geometric LSMs (test: reference) were included within the pre-defined range 80% to 125% (0.80, 1.25) for the PK parameters $AUC_{0-\infty}$, AUC_{0-t} , C_{max} and the area under the curve from time zero to 360 hours (AUC_{0-360h}) for all three treatment comparisons (FKB327 (Hulio) versus US-sourced Humira; Hulio (FKB327) versus EU-sourced Humira; and US-sourced Humira versus EU-sourced Humira). Values for the time of maximum concentration (t_{max}) were comparable between Hulio (FKB327) versus EU-sourced Humira; US-sourced Humira versus EU-sourced Humira; but the lower limit of the 90% CI for t_{max} for Hulio (FKB327) was outside the CI for US-sourced Humira. While the 90% CI for C_{max} and AUC_{0-360h} for Hulio (FKB327) were within the 90% CI for EU-sourced Humira, they fell entirely above unity).

Study FKB327-004 was a Phase I, randomised, active-controlled, single-blind, parallel-group clinical pharmacology study the aim of which was to compare the PK and safety of FKB327 (Hulio, adalimumab) and Humira (adalimumab) after a single dose, administered by SC injection, to healthy Japanese adult males. Both FKB327 and Humira (US-licensed) were administered using a pre-filled syringe. In this population, the 90% CIs of the geometric LSM ratios for C_{max} and AUC_{0-360h} were fully contained within the pre-defined similarity range of 0.80 to 1.25. However, for the third primary PK parameter, AUC_{0-t} , the upper limit of the 90% CI of the geometric LSM ratio (1.17; 90% CI: 1.05, 1.30) was outside the pre-defined similarity range (test: reference) as were the upper limits of the 90% CIs of the geometric LSM ratios for the secondary PK parameters $AUC_{0-\infty}$ and $t_{1/2}$.

Study FKB327-002 was a Phase III, multicentre, randomised, double-blind, parallel arm, active comparator, efficacy equivalence study, which also collected blood samples for PK studies. Blood samples were collected for the quantification of serum adalimumab concentration at Baseline (Week 0), prior to dosing at Weeks 2, 4, 12, 20, and at Week 24. The primary objective of the study was to assess the efficacy of FKB327 (Hulio, adalimumab), compared with Humira (adalimumab), when each was administered in combination with methotrexate. Serum was also collected for adalimumab concentrations and assessment of anti-drug antibody titres. During the comparison period, median values of Hulio (FKB327) and Humira were comparable, although the mean serum concentration of Hulio (FKB327) was higher than the mean serum concentration of Humira at each of the measurement time points. Between individual variability was high and the differences did not appear statistically significant. Samples for participants with high anti-drug antibody titres on the last sampling day appeared to show more variability in serum adalimumab concentrations, and generally lower serum adalimumab concentrations throughout the study, irrespective if they were treated with Hulio (FKB327) or Humira.

Over the whole PK program, the evaluator concluded that despite some individual inconsistencies, there were no notable differences in the PK parameters of FKB327 (Hulio, adalimumab) and US-licensed Humira (adalimumab). These inconsistencies were unlikely to indicate potential differences in clinical efficacy or safety.

Pharmacodynamics

No specific comparisons of the pharmacodynamics of FKB327 (Hulio, adalimumab) and Humira (adalimumab) were included in the dossier. The evaluator noted that in the clinical Study FKB327-002 and its extension Study FKB327-003 serum matrix metalloproteinase-3 concentrations were lower at a range of periods following treatment with either Hulio (FKB327) or Humira, compared to Baseline.

Efficacy

The primary study comparing the efficacy of FKB327 (Hulio, adalimumab) and Humira (adalimumab, US-licensed) was Study FKB327-002. FKB327 or Humira was administered every other week for 22 weeks to 728 adult patients with active rheumatoid arthritis who were receiving methotrexate at a stable dose (10 to 25 mg/kg) for a minimum of eight weeks prior to screening but required additional therapy to control rheumatoid arthritis. The primary efficacy outcome was the ACR20 response rate at Week 24.¹² The key secondary efficacy outcome was DAS28-CRP at Week 24;¹³ and several additional variables for supportive purposes.

The sample size was calculated to be sufficient to demonstrate equivalence of the ACR20 response rate for FKB327 (Hulio, adalimumab) and Humira (adalimumab) with 80% power, based on an equivalence margin of $\pm 13\%$, an estimated ACR20 response rate of 57% to 63%, and a maximum of 15% of study participants being ineligible for the per-protocol analysis. The 2-sided 95% CI for the difference in the ACR20 response rate between the two treatment groups needed to lie entirely within the bounds of -13% to +13% for bioequivalence to be demonstrated.

At Baseline, demographics and disease status in the two treatment groups were generally comparable. Overall, study participants were predominantly female (77.6%, 565/728), White (85.0%, 619/728) and aged less than 65 years (82.6%, 601/728). Participants were aged from 18 to 93 years inclusive with a mean (standard deviation, or SD) age of 53.3 (12.2) years. The mean counts of tender joints (TJC, 68 joint count and 28 joint count), swollen joints (SJC, 66 joint count and 28 joint count), patient's assessment of disease activity score, physician's assessment of disease activity score, patient's assessment of pain score and DAS28-ESR score;¹³ were similar in the two treatment groups. Mean values for the Health Assessment Questionnaire and DAS28-CRP were the same in each treatment group. The majority of randomised subjects had a screening DAS28-CRP > 5.1 (91.2%, 663/730 subjects) and had not received prior biological treatment for rheumatoid arthritis (81.9%, 598/730 subjects).

Based on the pre-defined equivalence limits required by the EMA's Committee on the Medicinal Products for Human Use (CHMP) and the US FDA, FKB327 (Hulio, adalimumab) demonstrated equivalent efficacy to US-sourced Humira (see following Table 5, below). Sensitivity analyses including non-responder imputation, multiple imputation and tipping point approaches supported the primary outcome.

¹² **ACR responses** (based on the American College of Rheumatology (ACR) criteria) are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a $\geq 20\%$ improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) $\geq 20\%$ improvement in 3 of the following 5 assessments - patient's assessment of pain (visual analog scale; VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ (Health Assessment Questionnaire) and CRP (C-reactive protein). ACR 50 and ACR 70 are similarly defined.

¹³ The **Disease Activity Score 28 (DAS28)** is a system developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of rheumatoid arthritis. Calculation of a DAS28 score involves the combination of an examination of 28 specified joints for tenderness upon touching and swelling, markers via blood sample, and the patient's subjective assessment of disease activity during the preceding 7 days on a scale between 0 ('no activity') and 100 ('highest activity possible'). DAS28 is often used in clinical trials for the development of rheumatoid arthritis (RA). DAS28 values range from 2.0 to 10.0; higher values mean a higher disease activity. Alternatives, such as the DAS28-CRP include the measurement of CRP (C-reactive protein) in combination with the DAS28; or ESR (erythrocyte sedimentation rate) in combination with the DAS28 (DAS28-ESR).

Table 4: Study FKB327-002, ACR20 response rate at Week 24 (full analysis set, per protocol; analysis set)

	FKB327	Humira	Total
FAS (root cause imputation)^a, N	363	358	721
Number of patients with an evaluable ACR20 response at Week 24	363	358	721
Patients achieving ACR20 response at Week 24			
n (%) ^b	270 (74.4)	271 (75.7)	541 (75.0)
95% CI ^c	69.6, 78.8	70.9, 80.1	71.7, 78.2
FKB327 – Humira ^d		-1.3	
95% CI		-7.6, 5.0	
95% CI contained in $\pm 13\%$ equivalence margin?		Yes	
FAS (non-responder imputation)^e, N	363	358	721
Number of patients with an evaluable ACR20 response at Week 24	363	358	721
Patients achieving ACR20 response at Week 24			
n (%) ^b	263 (72.5)	266 (74.3)	529 (73.4)
95% CI ^c	67.5, 77.0	69.4, 78.8	70.0, 76.6
FKB327 – Humira ^d		-1.8	
90% CI		-7.3, 3.6	
90% CI contained in -12% to +15% equivalence margin?		Yes	
PPAS, N	314	325	639
Number of patients with an evaluable ACR20 response at Week 24	314	325	639
Patients achieving ACR20 response at Week 24			
n (%) ^f	249 (79.3)	259 (79.7)	508 (79.5)
95% CI ^c	74.4, 83.6	74.9, 83.9	76.2, 82.6
FKB327 – Humira ^d		-0.4	
90% CI		-5.6, 4.9	
90% CI contained in -12% to +15% equivalence margin?		Yes	
95% CI		-6.7, 5.9	
95% CI contained in $\pm 13\%$ equivalence margin?		Yes	

ACR = American College of Rheumatology; CI = confidence interval, FAS = full analysis set, N = number of patients in full analysis set; n = total number of patients with observation; PPAS = per-protocol analysis, RA = rheumatoid arthritis.

a Missing responses for the ACR20 and responses for patients who discontinue the treatment prior to Week 24 were imputed as follows: if the patient withdrew due to lack of efficacy, withdrawal of consent, an adverse event (non-infection), medical reason (non-infection) or if the patient has taken a prohibited treatment for RA and has been withdrawn from study treatment, they were regarded as 'non-responders'; for all other patients with a missing ACR20 response at Week 24, last observation carried forward was used on the ACR to determine whether they were 'responders' or 'non-responders'.

b Percentages base on the number of patients with an evaluable ACR20 result at Week24, after imputation.

c 95% CI calculated using the Clopper-Pearson method.

d CI calculated using a normal approximation with no continuity correction.

e Missing Week 24 responses for the ACR and responses for patients who discontinued the treatment prior to Week 24 were imputed using non-responder imputation.

f Percentages are based on the number of patients with an evaluable ACR20 result at Week 24.

The ACR20 response rate is defined as a 20% improvement in tender and swollen joint counts and at least 3 out of 5 other indicators.

Safety

Study FKB327-002 was the primary source of clinical safety data. The open label extension study FKB327-003 provided supporting data. Adverse event reports were collected using patient report, physical examinations, electrocardiogram findings, chest x-ray reports and clinical laboratory tests. Adverse events of special interest (AESI) included infection, serious infections (including tuberculosis), malignancies and lymphoproliferative disorders, injection site reactions to study drug, hypersensitivity reactions and anaphylaxis to study drug, pancytopenia, aplastic anaemia, neutropenia,

thrombocytopenia, new or worsening congestive heart failure, demyelination and lupus-like reactions.

In Study FKB327-002, 74.3% (269/362) of the Humira (adalimumab) treatment group received all 12 scheduled doses of study treatment compared with 69.7% (255/366) of the FKB327 (Hulio adalimumab) treatment group. The dosage of each study treatment was 40 mg every other week administered SC. The mean number of doses of study drug received by participants in each treatment group was comparable (FKB327 treatment group: mean (standard deviation or SD) 11.4 (1.63); Humira treatment group: mean (SD) 11.3 (1.88)). In the FKB327 treatment group, 27.3% of participants (100/366) received delayed or interrupted dosing compared with 22.1% (80/362) of subjects in the Humira treatment group. Duration of treatment was comparable (FKB327 treatment group: mean (SD) 163.2 (22.30) days, median 168.0 days (range: 14 days, 191 days); Humira treatment group: mean (SD) 162.1 (25.79) days, median 168.0 days (range: 14 days, 185 days)). Overall exposure in patient-years was also comparable in the two treatment groups (FKB327 treatment group: 163.52 patient-years versus Humira treatment group: 160.63 patient-years).

In Study FKB327-002, the incidence rates of treatment emergent adverse events (TEAE) were similar for each treatment (FKB327 (Hulio, adalimumab: 2.00 events/patient-year; Humira, adalimumab: 2.69 events/patient-year). The incidence rate of severe TEAEs was higher in subjects treated with FKB327 (FKB327: 0.073 events/patient-year; Humira: 0.039 events/patient-year) with a notable difference in the rates of treatment-emergent severe adverse events falling in the 'Infections and infestations SOC' (or System Organ Class) (FKB327: 0.020 events/patient-year; Humira: 0.009 events/patient-year). The incidence rates of the TEAEs reported in the highest proportions of subjects were similar for the two treatments:

- nasopharyngitis:
 - FKB327 (Hulio, adalimumab) 13.0% (86/664) 0.13 events/patient-year versus Humira (adalimumab) 9.8% (46/470), 0.16 events/patient-year
- rheumatoid arthritis:
 - FKB327 (Hulio, adalimumab): 6.8% (45/664) 0.13 events/patient-year versus Humira (adalimumab): 4.9% (23/470), 0.09 events/patient-year
- upper respiratory tract infection:
 - FKB327 (Hulio, adalimumab): 5.7% (38/664), 0.05 events/patient-year versus Humira (adalimumab): 5.5% (26/470), 0.08 events/patient-year
- bronchitis:
 - FKB327 (Hulio, adalimumab): 5.3% (35/664), 0.05 events/patient-year versus Humira (adalimumab): 5.7% (46/470), 0.09 events/patient-year.

By SOC, the event incidence rates were generally comparable for subjects receiving FKB327 (Hulio, adalimumab) compared to subjects receiving Humira, adalimumab. Of note, the incidence rate of events falling under the 'Gastrointestinal disorders' SOC was lower in subjects receiving the FKB327 compared with Humira (0.11 events/patient-year versus 0.21 events/patient-year) as were events falling under the 'Infections and infestations' SOC (0.63 events/patient-year versus 0.80 events/patient-year). The incidence rate of events in the 'Vascular disorders' SOC was also lower in subjects receiving FKB327 compared with Humira (0.05 events/patient-year versus 0.10 events/patient-year) due to a higher incidence rate of hypertension in subjects receiving Humira (0.03 events/patient-year versus 0.07 events/patient-year).

Table 5: Study FKB327-002, treatment emergent adverse events reported for $\geq 1\%$ of subjects in either treatment group (safety analysis set)

System Organ Class Preferred Term	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Number of patients with at least 1 TEAE with incidence in $\geq 1\%$ of patients	123 (33.6)	146 (40.3)	269 (37.0)
Infections and infestations	106 (29.0)	108 (29.8)	214 (29.4)
Nasopharyngitis	26 (7.1)	29 (8.0)	55 (7.6)
Upper respiratory tract infection	13 (3.6)	18 (5.0)	31 (4.3)
Urinary tract infection	17 (4.6)	11 (3.0)	28 (3.8)
Bronchitis	4 (1.1)	14 (3.9)	18 (2.5)
Pharyngitis	5 (1.4)	9 (2.5)	14 (1.9)
Oral herpes	6 (1.6)	7 (1.9)	13 (1.8)
Latent tuberculosis	8 (2.2)	4 (1.1)	12 (1.6)
Gastrointestinal disorders	34 (9.3)	41 (11.3)	75 (10.3)
Diarrhoea	11 (3.0)	13 (3.6)	24 (3.3)
Nausea	7 (1.9)	5 (1.4)	12 (1.6)
Musculoskeletal and connective tissue disorders	33 (9.0)	38 (10.5)	71 (9.8)
Rheumatoid arthritis	12 (3.3)	9 (2.5)	21 (2.9)
Back pain	9 (2.5)	5 (1.4)	14 (1.9)
Arthralgia	4 (1.1)	4 (1.1)	8 (1.1)
Metabolism and nutrition disorders	32 (8.7)	24 (6.6)	56 (7.7)
Hypercholesterolaemia	15 (4.1)	11 (3.0)	26 (3.6)
Dyslipidaemia	7 (1.9)	4 (1.1)	11 (1.5)
Skin and subcutaneous tissue disorders	29 (7.9)	23 (6.4)	52 (7.1)
Rash	6 (1.6)	4 (1.1)	10 (1.4)
Investigations	28 (7.7)	21 (5.8)	49 (6.7)
Alanine aminotransferase increased	4 (1.1)	6 (1.7)	10 (1.4)
General disorders and administration site conditions	19 (5.2)	22 (6.1)	41 (5.6)
Injection site erythema	5 (1.4)	8 (2.2)	13 (1.8)
Injection site reaction	3 (0.8)	5 (1.4)	8 (1.1)
Nervous system disorders	18 (4.9)	23 (6.4)	41 (5.6)
Headache	6 (1.6)	10 (2.8)	16 (2.2)
Blood and lymphatic system disorders	17 (4.6)	17 (4.7)	34 (4.7)
Anaemia	9 (2.5)	10 (2.8)	19 (2.6)
Vascular disorders	17 (4.6)	17 (4.7)	34 (4.7)
Hypertension	7 (1.9)	14 (3.9)	21 (2.9)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in safety analysis set; n = total number of patients with observation; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment emergent adverse event.

Events ordered per overall SOC frequency.

Percentages based on the number of patients in the safety analysis set.

TEAE were defined as AEs that started or increased in severity after the first study medication administration.

Each patient was counted only once within each SOC and PT.

TEAE were coded using MedDRA Version 17.1.

In the open-label extension study, subjects who received FKB327 (Hulio, adalimumab) had a lower incidence rate of TEAEs (1.707 events/patient-year) compared with those who received Humira adalimumab (2.075 events/patient-year). With regard to TEAEs of special interest, the incidence rates of infections, and serious infections, respectively, in subjects receiving FKB 327 and Humira were generally comparable during the study.

The evaluator concluded that the types and frequencies of adverse effects reported in study participants receiving FKB327 (Hulio, adalimumab) and Humira adalimumab were generally comparable in the submitted studies. There were no notable differences in the safety findings for FKB327 and Humira in the equivalence study, Study FKB327-002.

Differences in the proportions of participants with specific adverse events were based on small absolute numbers reporting the event and did not suggest that the safety profile of the two products was different. The immunogenicity of FKB327 was similar to that of Humira and is considered acceptable based on the information provided. The proportion of participants who developed anti-drug antibodies (ADA) and neutralising antibodies (nAb), respectively, were similar in participants receiving FKB327 and Humira in each of the studies in which immunogenicity was assessed, and there were no notable differences

between the treatment groups in regard to the effect of ADAs and nAbs on efficacy and safety. The ADA titres recorded for each treatment were also similar.

Clinical evaluator's recommendation

The clinical evaluator recommended that inclusion of a pack insert based on the PI document is a condition of registration, as has been required for other adalimumab products.

Risk management plan

The reviewed risk management plan (RMP) documents include the EU-RMP version 3.0 dated 31 May 2019; data lock point (DLP) 18 February 2019, and subsequently version 3.2 dated 6 August 2020; DLP 24 December 2019, and the Australian-specific annex (ASA) version 1.0 dated 3 April 2020, and subsequently the ASA versions 2.0 (18 December 2020) and 3.0 (22 February 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.¹⁴

Table 6: Sponsor's summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Serious infections	✓‡	✓*	✓	✓†
	Tuberculosis (TB)	✓‡	✓*	✓	✓†
	Malignancies	✓‡	✓*	✓	✓†
	Demyelinating disorders (including multiple sclerosis (MS), Guillain-Barré syndrome (GBS), and optic neuritis (ON))	✓	–	✓	✓†
	Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with in utero exposure to Hulo	✓	–	✓	✓†
	Progressive multifocal leukoencephalopathy (PML)	✓	–	✓	–

¹⁴ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Reversible posterior leukoencephalopathy syndrome (RPLS)	✓	–	✓	–
	Adenocarcinoma of colon in ulcerative colitis patients	✓	–	✓	–
Missing information	Patients with immune-compromised conditions	✓	–	✓	–
	Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease	✓	–	✓	–
	Episodic treatment in psoriasis, ulcerative colitis and juvenile idiopathic arthritis	✓	–	✓	–
	Long-term safety information in the treatment of children with uveitis	✓	–	✓	–

*Patient registry monitoring; † Patient reminder card; ‡ Targeted follow up questionnaire

The RMP evaluator concluded that the proposed summary of safety concerns aligns with the innovator. Routine pharmacovigilance activities and routine risk minimisation activities are planned for all safety concerns. All issues raised by the RMP evaluation were satisfactorily addressed.

RMP evaluator recommendations regarding 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 Hulio EU-Risk Management Plan (RMP) (version 3.2, dated 6 August 2020, data lock point 24 December 2019), with Australian Specific Annex (version 3.0, dated 22 February 2021), included with submission PM-2020-01807-1-3, 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 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

The sponsor has provided sufficient evidence to support the claim that the physicochemical and biological characteristics of Hulio, adalimumab (FKB327) are comparable to those of the Australian innovator product Humira, adalimumab. The nonclinical evaluation concluded that there were no clinically meaningful differences between Hulio and Humira identified in the submitted comparative pharmacology, pharmacokinetic and toxicity studies, and the clinical evaluation concluded that the clinical safety and efficacy of Hulio were also comparable to Humira.

Proposed action

The Delegate proposes to approve the registration of the biosimilar product Hulio (adalimumab) 40mg/0.8 mL solution for injection auto-injector pen, 40mg/0.8 mL solution for injection pre-filled syringe, and 20mg/0.4 mL solution for injection pre-filled syringe, for the same indications as have been approved for the Australian reference product Humira (adalimumab)

The Delegate also proposes to impose the following additional conditions of registration:

- All batches of Hulio supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
- 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.
- A 'pack insert' (being an abbreviated version of the TGA-approved Hulio Product Information) in a format acceptable to the TGA, or the approved Product Information, must be included with the products as a package insert.
- Where a 'pack insert' is provided as a package insert, there is a continuing obligation on the sponsor to ensure that the content is consistent with the PI.

Advisory Committee considerations¹⁵

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

¹⁵ 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

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Hulio (adalimumab) 40 mg/0.8 mL; and 20 mg/0.4 mL, solution for injection, pre-filled pen/syringe, indicated for:

Rheumatoid arthritis

Hulio 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.

Hulio can be used alone or in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular Juvenile Idiopathic Arthritis

Hulio 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 antirheumatic drugs (DMARDs). HULIO can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-related arthritis

Hulio 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

Hulio 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

Hulio is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's Disease in Adults and Children (≥ 6 years)

Hulio is 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

Hulio is 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 5.1 Pharmacodynamic Properties -Clinical Trials).

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.

Psoriasis in adults and children

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

Hulio 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)

Hulio 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

Hulio 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.

Specific conditions of registration applying to these goods

- The Hulio EU-RMP (version 3.2, dated 6 August 2020, DLP 24 December 2019), with ASA (version 3.0, dated 22 February 2021), included with submission PM-2020-01807-1-3, 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 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

- All batches of Hulio supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.

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 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.

The CPD should be emailed to biochemistry.testing@health.gov.au as a single PDF document.

- For all Hulio products, either:
 - a pack insert (being an abbreviated version of the TGA-approved Hulio PI) in a format acceptable to the TGA, or
 - the approved PI, must be included with the products as a package insert.

Where a pack insert is provided as a package insert, there is a continuing obligation on the sponsor to ensure that the content is consistent with the PI.

Attachment 1. Product Information

The PI for Hulio 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>](https://www.tga.gov.au/product-information-pi).

Therapeutic Goods Administration

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<https://www.tga.gov.au>