5.13 ADALIMUMAB
Injection 40 mg in 0.8 mL pre-filled syringe, Injection 40 mg in 0.8 mL single dose autoinjector, Hadlima®, Merck Sharp & Dohme (Australia) Pty Ltd

1 Purpose of Application

1.1 The minor submission requested an Authority Required (Section 85) listing of a biosimilar brand of adalimumab, Hadlima®, for the rheumatoid arthritis indication for which the reference biological (Humira®) is currently PBS listed.

2 Requested listing

2.1 The submission requested the following new listing.

2.2 The requested dispensed price for maximum quantity was calculated based on the current list price for Humira® and accounting for the 25% statutory price reduction that would occur if Hadlima® is listed on the PBS.

Initial treatment

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ADALIMUMAB 40 mg/0.8 mL injection, 2 x 0.8 mL cartridges 40 mg/0.8 mL injection, 2 x 0.8 mL syringes	1	3	$1070.67	Hadlima Merck Sharp & Dohme

Continuing treatment

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ADALIMUMAB *40 mg/0.8 mL injection, 2 x 0.8 mL cartridges* *40 mg/0.8 mL injection, 2 x 0.8 mL syringes*	1	5	$1070.67	Hadlima Merck Sharp & Dohme

2.3 In accordance with the Government's biosimilar uptake measures, the sponsor proposed the following uptake drivers:

- A change to the prescribing software that gives preference to the biosimilar for patients naïve to treatment with adalimumab; and
- Streamlined authority for patients continuing (i.e. at the subsequent continuing phase) on biosimilar adalimumab.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Background

3.1 Hadlima® was approved by the TGA for rheumatoid arthritis on 24 January 2018, and was determined to be a biosimilar to the reference brand Humira®.

3.2 Hadlima® has not previously been considered by the PBAC.

Brand equivalence and substitution at the pharmacist level ('a' flagging)

3.3 The Schedule of Pharmaceutical Benefits provide the following definition of brand equivalence:

> **Extract from the Explanatory Notes to the PBS Schedule[1]**
>
> **BRAND EQUIVALENCE**
>
> 'a' located immediately before brand names of a particular strength of an item indicates that the sponsors of these brands have submitted evidence that they have been demonstrated to be bioequivalent or therapeutically equivalent, or that justification for not needing bioequivalence or therapeutic equivalence data has been provided to and accepted by the Therapeutic Goods Administration. It would thus be expected that these brands may be interchanged without differences in clinical effect.

3.4 Many medicines are available on the PBS in different brands. The Schedule of Pharmaceutical Benefits indicates where different brands are considered equivalent for the purposes of substitution at the point of dispensing by using 'a' flags.

3.5 The ability for prescribers and pharmacists to substitute generic or biosimilar brands for originator brands is an important part of encouraging use of generics and biosimilars in the marketplace and adds to the sustainability of the PBS.

3.6 For any individual prescription, a prescriber may choose to not permit brand substitution by indicating 'substitution not permitted' on the prescription. Likewise, when substitution is permitted, a patient may nominate which 'a' flagged brand they wish to receive from the pharmacist, except when State or Territory Law prohibits substitution (e.g. for Schedule 8 drugs of dependence). The substitution process allows for patient and prescriber choice and is not automatic.

3.7 The *National Health Act* 1953 ("The Act") makes it an offence for a pharmacist to supply a pharmaceutical benefit other than the benefit directed to be supplied in a prescription except when, amongst other criteria, the Schedule issued by the Department of Health states that the specified benefit and the substitute benefit are equivalent.

[1] Symbols used in the Schedule - http://www.pbs.gov.au/info/healthpro/explanatory-notes/section2/section-2-symbols

3.8 At the March 2018 meeting, the PBAC advised that the following revised considerations will be used to make a recommendation on brand equivalence ('a' flagged) of biosimilars with the reference brand;

- The Therapeutic Goods Administration has determined that the product is a biosimilar of the reference medicine as evidenced by ARTG registration documentation;
- Availability of supportive data relating to the effects of switching between the reference product and the biosimilar product/s; and
- Practical considerations relating to substitution by the pharmacist at the point of dispensing. This includes strength of formulation, number of units per pack and maximum quantities between the brands, which may make substitution at the pharmacy level difficult from a practical perspective.

3.9 The PBAC considered that where a biosimilar product could not be recommended to be brand equivalent ('a' flagged) at the time of PBS listing, data should be collected to support this consideration at a later point.

3.10 If the PBAC provides advice on brand equivalence ('a' flagging), the decision to apply brand equivalence to listings in the Schedule is made by the Minister for Health (or Delegate).

Biosimilar uptake measures

3.11 The biosimilar uptake measures were agreed as part of the strategic agreements that the Government reached with Medicines Australia, the Generic and Biosimilar Medicines Association and the Pharmacy Guild of Australia as part of the 2017 Budget process.

3.12 The PBAC will advise whether implementation of the uptake drivers is likely to raise any clinical or other concerns about appropriate use on the PBS. The PBAC may, on a case-by-case basis, provide advice relating to:

- encouraging the prescribing of a biosimilar brand for treatment naïve patients; and
- applying a lower level of authority to biosimilar brand(s) than exists for the reference brand of biological medicines.

3.13 After PBAC advice is received, a decision will be made about applying the drivers for the relevant medicine. The policy provides for lower authority requirements only for biosimilar brands, but there will be no increase in authority requirements to prescribe reference brands.

3.14 The PBAC has previously stated it had no concerns about encouraging prescribing of a biosimilar brand rather than the reference biological agent brand for treatment naïve patients, including through notes in the Schedule and prescribing software changes. (Etanercept (Brenzys) Public Summary Document, August 2017 PBAC Meeting).

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted and welcomed the input from an individual (1) via the Consumer Comments facility on the PBS website.

Clinical trials

4.3 The sponsor presented one pivotal trial that was used in the regulatory dossier submission to the TGA, comparing the efficacy and safety of Hadlima® with Humira® in patients with rheumatoid arthritis.

4.4 The sponsor provided the product information (PI) for Hadlima®, which presented the following information regarding the efficacy and safety findings of the phase 3 randomised, double-blind, parallel group, multicentre, clinical trial in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy.

4.5 The primary efficacy endpoint, ACR20 response rate at Week 24, was equivalent in the Hadlima® and Humira® treatment group. The adjusted treatment difference in ACR20 response rate at Week 24 was 0.1% and the 95% confidence interval (CI) of the adjusted treatment difference was [−7.83%, 8.13%] which was completely contained within the pre-defined equivalence margin of [−15%, 15%]. The secondary efficacy endpoints (ACR50, ACR70, DAS28, EULAR response) at Week 24 were also comparable between the treatment arms.

4.6 At Week 24, 254 patients receiving Humira® were randomised to either continue on Humira® or be transitioned to Hadlima® up to Week 50. In anti-drug antibody positive patients, the ACR20 response rate at Week 24 was lower in the Hadlima® treatment group than in the Humira® treatment group (57.5% and 71.2%, respectively), while the ACR50 response rates were 28.8% and 35.6%, and the ACR 70 response rates were 19.2% and 16.4% in the Hadlima® and the Humira® treatment groups, respectively. The ACR20 response rates at Week 52 in ADA positive patients were 67.1%, 82.1%, and 76.2% in the Hadlima®, Humira®/Hadlima®, and Humira®/Humira® treatment groups, respectively. However the study was not powered to detect differences in these smaller sub groups. The incidence of treatment-emergent adverse events (TEAEs) up to Week 24 were 35.8% and 40.7% in the Hadlima® and Humira® treatment groups, respectively. The incidence of TEAEs up to Week 52 were 52.2%, 56.4%, and 54.3% in the Hadlima®, Humira® overall, and Humira®/Humira® treatment groups, respectively. After 24 weeks, the overall

incidence of TEAEs reported were Hadlima®/Hadlima® (32.3%), Humira®/Hadlima® (37.6%) and Humira®/Humira® (33.1%).

Table 1. Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
SB5-G31-RA	A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy	**N/A**

Source: the submission

Clinical claim

4.7 Based on the results of the trial, the sponsor claimed that Hadlima® was equivalent to Humira® with respect to efficacy and at least as safe as Humira®.

4.8 The PBAC considered that the claim of non-inferior comparative safety and effectiveness was reasonable.

Estimated PBS usage & financial implications

4.9 The submission stated that listing Hadlima® would confer cost savings to the PBS as it would trigger a 25% statutory price reduction to the ex-manufacturer price of Humira®, but did not attempt to quantify the savings.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the adalimumab biosimilar (Hadlima®) be listed on the General Schedule (Section 85) for the rheumatoid arthritis (RA) indication for which the reference product Humira® is currently PBS listed.

5.2 The PBAC noted the efficacy and safety findings of the pivotal trial used in the regulatory dossier to the TGA, and were satisfied that the results demonstrated that Hadlima® was non-inferior to Humira® in terms of both efficacy and safety.

5.3 In Australia, decisions about indication extrapolation for biosimilar medicines are made by the Therapeutic Goods Administration. The PBAC noted that rheumatoid arthritis is the only TGA-approved indication for Hadlima®, and that the sponsor had not sought to have Hadlima® TGA-registered for the remaining Humira-approved indications at this time. The PBAC foreshadowed that if Hadlima® is TGA registered for any or all of the remaining Humira® indications in the future and the sponsor requests PBS listing for those indications, the submission would require minimal review.

5.4 The PBAC advised that there were no clinical or other concerns about appropriate use of medicines if the policy decision were made to apply the following uptake

drivers to the RA indication, as proposed by the sponsor:

- a change to the prescribing software that gives preference to the biosimilar for patients naïve to treatment with adalimumab (this currently equates to the addition of an administrative note encouraging the prescribing of the biosimilar brand in treatment naïve patients); and
- streamlined authority for patients continuing (i.e. subsequent continuing) on biosimilar adalimumab;

5.5 The PBAC noted that another adalimumab biosimilar brand, Amgevita®, was also considered at its July 2018 PBAC meeting, with Humira® as the reference product. The PBAC considered it would be appropriate for all three brands of adalimumab (Humira®, Amgevita® and Hadlima®) to be marked as equivalent ('a' flagged) to each other in the Schedule of Pharmaceutical Benefits.

5.6 The PBAC advised that, under Section 101 (4AACD) of the *National Health Act, 1953*, the Hadlima® and Humira® brands of adalimumab could be marked as equivalent in the Schedule of Pharmaceutical Benefits for the purposes of substitution at the pharmacy level.

5.7 The PBAC noted the difference in injection device between Hadlima® and Humira®. The PBAC recalled that it had encountered this issue in its consideration of the etanercept biosimilar, Brenzys®, and stated in that case that differences in auto injector presentations were 'likely to be minor and can be managed through the regular patient education and counselling on the use of the devices that is provided to patients by prescribers and pharmacists.' (etanercept public summary document, July 2016). The PBAC considered that a similar conclusion applies to adalimumab.

5.8 The PBAC reiterated its previous advice that adalimumab should not be exempt from the Early Supply Rule.

5.9 The PBAC reiterated its previous advice that adalimumab is not suitable for prescribing by nurse practitioners.

5.10 The PBAC noted that this submission is not eligible for independent review as it received a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 Add new brand with schedule equivalence ('a' flag) for the same RA indication as for Humira®.

6.2 Restrictions to be revised to apply the biosimilar uptake measures for initial (Initial 1 and Initial 2) and continuing (First continuing and Subsequent continuing) treatment restrictions for RA. The lower Streamlined authority level will apply to Subsequent continuing treatment only. The full restriction wording will be based upon the RA

restriction for the etanercept and infliximab biosimilars, which are currently being finalised.

6.3 Addition of an administrative note encouraging biosimilar prescribing for treatment naïve patients.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

The sponsor had no comment.