

5.07 ADALIMUMAB

Injection 40 mg in 0.8 mL pre-filled syringe

Injection 40 mg in 0.8 mL pre-filled pen

Hyrimoz[®],

Sandoz Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor submission sought an Authority Required listing for a new biosimilar brand of adalimumab (Hyrimoz[®]) in the form of 40 mg/0.8 mL pre-filled syringe and 40 mg/0.8 mL pre-filled pen.

2 Requested listing

- 2.1 The submission requested General PBS schedule listings (Section 85) of Hyrimoz for all indications for which the reference brand, Humira[®], is PBS-listed, except those for paediatric patients with certain conditions which require dosing of less than 40 mg (see paragraph 2.3).
- 2.2 The proposed PBS indications for Hyrimoz were:
- Severe Crohn disease
 - Moderate to severe ulcerative colitis
 - Severe active juvenile idiopathic arthritis
 - Complex refractory Fistulising Crohn disease
 - Severe active rheumatoid arthritis
 - Severe psoriatic arthritis
 - Ankylosing spondylitis
 - Severe chronic plaque psoriasis
 - Moderate to severe hidradenitis suppurativa
- 2.3 The sponsor of Hyrimoz did not pursue PBS listings for the following Humira indications due to the absence of a 20 mg/0.4 mL injection presentation of Hyrimoz:
- Paediatric patients with severe Crohn disease: treatment for patients weighing less than 40 kg (Humira PBS codes 10389T, 10396E, 10422M)
 - Patients with moderate to severe ulcerative colitis: treatment for patients weighing less than 40 kg (Humira PBS codes 11121H, 11127P)
 - Patients with severe juvenile idiopathic arthritis: treatment for patients weighing less than 30 kg (Humira PBS codes 9661L, 9678J)
- 2.4 The sponsor included pack sizes of 6 pre-filled pens/syringes in its requested listings in case this pack size becomes available for Hyrimoz. However, the minor submission stated that the sponsor intended to supply only the pack size of 2 pens/syringes.

Where Humira has pack sizes of 4 and 6 listed for certain treatment phases and conditions, the sponsor has proposed listing Hyrimoz with increased maximum quantities to provide the same number of injections (i.e. maximum quantities of 2 and 3 in place of a 4-pack and 6-pack, respectively).

- 2.5 The submission proposed splitting the continuing treatment restrictions for Hyrimoz into ‘first continuing’ and ‘subsequent continuing’ restrictions, with ‘first continuing’ scripts to be written authority (as is the case for Humira) and ‘subsequent continuing’ scripts to be streamlined authority (a lower authority level than Humira). This is in line with one of the biosimilar uptake drivers in the Government’s Biosimilar Awareness Initiative, which recommends that a lower level of authority be applied to biosimilar brands to encourage uptake by prescribers. At its July 2018 meeting, the PBAC recommended to list two other biosimilar brands of adalimumab, Amgevita and Hadlima, with the same biosimilar uptake driver applied (items 5.12 and 5.13, July 2018 Public Summary Document (PSD)). The minor submission proposed that initial restrictions should remain written authorities for both Hyrimoz and Humira.

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

3 Background

Registration status

- 3.1 Hyrimoz was TGA approved on 23 August 2018, and was determined to be a biosimilar to the reference brand Humira.

Previous PBAC consideration

- 3.2 This is the first PBAC submission for this biosimilar brand of adalimumab.
- 3.3 At its July 2018 meeting, the PBAC recommended two other biosimilar brands of adalimumab, Hadlima and Amgevita, for listing on the PBS. As of February 2020, neither of these brands was listed on the PBS.

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

4 Comparator

- 4.1 The minor submission nominated the reference brand of adalimumab, Humira, as the main comparator, which was appropriate.

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

5 Consideration of the evidence

Sponsor hearing

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

Consumer comments

5.2 The PBAC noted and welcomed the comments received from Crohn’s & Colitis Australia (CCA). The CCA advised that an individual patient had reported reduced pain and irritation while using another biosimilar brand compared to the originator brand Humira.

Clinical trials

5.3 As this was a minor submission, no evaluation of the clinical evidence was undertaken.

5.4 Details of the studies presented in the submission are provided in the table below.

Table 1. Studies presented in the submission

Trial ID (Full Study No.)	Protocol title/publication title	Publication citation
Supporting clinical studies (Module 2.5 – Clinical overview)		
Direct randomised trial(s)		
GP17-101 (supportive PK study)	A single-centre, randomised, double-blind, single-dose, three-arm, parallel group study in 219 healthy male and female subjects. Objective: to demonstrate PK bioequivalence of Hyrimoz, Humira (EU) and Humira (US) in terms of C_{max} and AUC_{0-inf} and AUC_{0-last} after a single s.c. injection of 40 mg of adalimumab	Clinical Study Report Report date: 11-May-2017
GP17-102 (supportive PK study – device development)	A single-centre, randomised, open-label, single-dose, two-arm, parallel group study in 108 healthy male subjects Objective: to describe PK of Hyrimoz administered by autoinjector or pre-filled syringe (PFS) as a single s.c injection of 40mg to healthy adult male subjects with body weights between 50 and 94.9kg in terms of AUC_{0-360h} (device comparison).	Clinical Study Report Report date: 11-May-2017
GP17-103 (supportive PK study – technical transfer)	A multi-centre, randomised, double-blind, parallel group, two-arm study in 178 healthy male subjects Objective: to demonstrate PK bioequivalence (90% CI of ratio of geometric means within the margins of [0.8; 1.25]) of Hyrimoz-Cook and Hyrimoz-Schaftenau in terms of C_{max} , AUC_{0-inf} and AUC_{0-last} after a single s.c. injection of 40 mg of adalimumab.	Clinical Study Report Report date: 11-May-2017
GP17-104 (pivotal PK study)	A single-centre, randomized, double-blind, single-dose, three-arm, parallel group study in 318 healthy male subjects comparing Hyrimoz with Humira (EU) and Humira (EU) with Humira (US). Objective: To demonstrate PK bioequivalence (90% CI of ratio of geometric means within the margins of [0.8; 1.25]) of Hyrimoz and Humira (EU), and PK bioequivalence of Humira (EU) and Humira (US) in terms of C_{max} and AUC_{0-inf} after a single s.c. injection of 40 mg of adalimumab	Clinical Study Report Report date: 11-May-2017

Trial ID (Full Study No.)	Protocol title/publication title	Publication citation
GP17-301 (pivotal confirmatory efficacy and safety study)	<p>A multi-center, randomized, double-blind, comparator-controlled study with treatment switches in 465 male and female patients with moderate to severe chronic plaque-type psoriasis. Patients enrolled in the EU received either Hyrimoz or Humira (EU), and patients enrolled in the US received either Hyrimoz or Humira (US).</p> <p>Objective: To demonstrate equivalent efficacy of Hyrimoz and Humira with respect to PASI75 response rate at Week 16 and similar safety and immunogenicity in patients with moderate to severe chronic plaque-type psoriasis</p>	<p>Clinical Study Report</p> <p>Report date: 11-May-2017</p>

Comparative effectiveness

- 5.5 The bioequivalence criteria for Hyrimoz were not met in Study GP17-101 due to underpowering. Study GP17-104 had a nearly identical methodology to Study GP17-101 but with a larger sample size. The pooled results from studies GP17-101 and GP17-104 were used to support the sponsor’s claim that Hyrimoz was bioequivalent to Humira (see paragraph 5.9).
- 5.6 In study GP-102, the pharmacokinetics of Hyrimoz administered by pre-filled syringe or autoinjector were examined. The TGA Evaluator concluded that, overall, the bioequivalence criteria comparing the pre-filled syringe and autoinjector were met.
- 5.7 Study GP17-103 was an assessment of bioequivalence between different manufacturing sites (Hyrimoz-Cook and Hyrimoz-Schaftenau). The TGA Evaluator concluded that the results supported bioequivalence between the two sites.
- 5.8 In study GP17-104, healthy subjects were administered with a single dose of Hyrimoz, Humira (EU) or Humira (US). The adalimumab concentration-time profiles were similar in all three treatment groups. The 90% CI of the geometric mean ratios for the primary PK parameters C_{max} and AUC_{0-inf} were within the standard bioequivalence interval of 0.8-1.25. The TGA Evaluator concluded that the bioequivalence criteria were met.
- 5.9 Study GP17-301 was a phase II, multi-centre, randomised, double-blind, comparator-controlled study with treatment switches in patients with moderate to severe chronic plaque-type psoriasis to compare Hyrimoz and Humira. The TGA Evaluator concluded that the results of this study supported the clinical efficacy of Hyrimoz in psoriasis, and also the biosimilarity of Hyrimoz to Humira.

Comparative harms

- 5.10 Overall, the TGA Evaluator concluded that the safety data from the clinical and pharmacokinetic studies demonstrated that there were no clinically meaningful differences in safety between Hyrimoz and Humira.

Clinical claim

- 5.11 The minor submission's clinical claim was that Hyrimoz is non-inferior in terms of efficacy and safety to Humira. The TGA Evaluator found that the results of the clinical and pharmacokinetic studies showed that the two products were similar in terms of both efficacy and safety and were biosimilar to one other.
- 5.12 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 5.13 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Estimated PBS usage & financial implications

- 5.14 The minor submission requested listing of Hyrimoz on a cost-minimisation basis to Humira.
- 5.15 The minor submission estimated that the financial impact to the PBS of listing Hyrimoz as the first alternative brand of adalimumab would be a minimum saving of more than \$100 million over six years. Including the potential impact of removal of the Special Pricing Arrangement with Humira (estimated rebate 28%, see paragraph 5.16) and price disclosure cuts, the minor submission estimated that the savings could be approximately more than \$100 million over six years.
- 5.16 In formulating the estimated savings, the sponsor made the following assumptions:
- Hyrimoz will be the first additional brand of adalimumab listed on the PBS, triggering a move of the drug to F2 and a statutory 25% price reduction.
 - A 6.6% annual growth rate for adalimumab services, based on the average annual historical growth rate for Humira from 2017-2019.
 - Adalimumab will take a 5% F1 anniversary price cut on 1 April 2020 (prior to the listing of Hyrimoz).
 - Adalimumab will experience a price disclosure impact consistent with that of infliximab. Based on a potential listing date of 1 August 2020, this would involve cuts of 12% on 1 April 2022 (cycle 2), 12% on 1 April 2023 (cycle 4) and 29% on the removal of the originator brand on 1 April 2024 (cycle 6). These all fall within Years 1-6 of the proposed listing.
 - The existing SPA rebate for Humira, which would be removed once Hyrimoz is PBS listed, was estimated to be 28% in line with the assumption in the Amgevita submission. This was based on the revealed rebate when etanercept moved from F1 to F2 (Amgevita PSD, July 2018).
 - The expected price reductions have been applied directly to the Humira net DPMQ. The baseline net DPMQ was calculated by dividing PBS benefits by PBS services for the current calendar year. The net DPMQ was used instead of the AEMP to avoid the need to project future usage at pack level (as different pack sizes have different DPMQs)

and to avoid the need to estimate future wholesale and pharmacy fees and mark-ups and patient co-payments.

5.17 As a minor submission, the financial estimates have not been independently evaluated.

5.18 The PBAC noted that the estimated savings were highly uncertain.

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

6 PBAC Outcome

6.1 The PBAC recommended the listing of adalimumab (Hyrimoz®) as a biosimilar brand of Humira on the General Schedule (Section 85) for the following indications on the basis of cost-minimisation with Humira:

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

6.2 The PBAC noted that the sponsor of Hyrimoz had not pursued PBS listing for the following indications due to the absence of a 20 mg/0.4 mL injection presentation of Hyrimoz:

- Paediatric patients with severe Crohn disease: treatment for patients weighing less than 40 kg (Humira PBS codes 10389T, 10396E, 10422M)
- Patients with moderate to severe ulcerative colitis: treatment for patients weighing less than 40 kg (Humira PBS codes 11121H, 11127P)
- Patients with severe juvenile idiopathic arthritis: treatment for patients weighing less than 30 kg (Humira PBS codes 9661L, 9678J)

6.3 The PBAC noted that the TGA Evaluator found that the results of the clinical and pharmacokinetic studies showed that Hyrimoz and the reference brand, Humira®, were similar in terms of both efficacy and safety and were biosimilar to one another.

6.4 The PBAC noted that the sponsor intended to supply only the pack size of 2 pens/syringes. Where Humira has pack sizes of 4 and 6 listed for certain treatment phases and condition, the PBAC considered that it is appropriate to list Hyrimoz with equivalent maximum quantity units to provide the same number of injections (i.e. maximum pack quantities of 2 and 3 in place of 4-pack and 6-pack, respectively).

6.5 The PBAC recalled that the Committee recommended the listing of two other brands

of adalimumab (Amegevita® and Hadlima®) in July 2018, and noted that these brands had not yet been listed on the PBS.

- 6.6 The PBAC considered that the following biosimilar uptake drivers should be applied to Hyrimoz, consistent with its previous recommendations regarding the application of these drivers to other biosimilar brands of adalimumab:
- Retain the initial 1 and 2 restrictions as Authority Required (written) benefits; and
 - Split the continuation criteria into ‘first continuing’ and ‘subsequent continuing’, to allow for the subsequent continuing restriction for the biosimilar to be Streamlined Authority while subsequent continuing restriction for the reference biological medicine will remain as a written authority; and
 - The application of the following Administrative Note encouraging the use of biosimilar brands for treatment of naïve patients.

Note

Biosimilar prescribing policy

Prescribing of the biosimilar brand, [brand name/s], is encouraged for treatment naïve patients.

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

- 6.7 The PBAC reiterated its previous advice that adalimumab is not suitable for nurse practitioner prescribing.
- 6.8 The PBAC has previously considered that adalimumab should not be exempt from the Early Supply Rule.
- 6.9 The PBAC advised that, under Section 101(4AACD) of the *National Health Act 1953*, in the Schedule of Pharmaceutical Benefits, Amegevita, Hadlima, Hyrimoz and Humira pre-filled syringes should be treated as equivalent to each other and Amegevita, Hadlima, Hyrimoz and Humira pre-filled pens should be treated equivalent to each other for the purpose of substitution (i.e., ‘a’ flagged in Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purpose of substitution).
- 6.10 The PBAC noted that this submission is not eligible for Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new adalimumab brand with schedule equivalence ('a' flag) for the same indications as Humira, except for:

- Paediatric patients with severe Crohn disease: treatment for patients weighing less than 40 kg (Humira PBS codes 10389T, 10396E, 10422M)
- Patients with moderate to severe ulcerative colitis: treatment for patients weighing less than 40 kg (Humira PBS codes 11121H, 11127P)
- Patients with severe juvenile idiopathic arthritis: treatment for patients weighing less than 30 kg (Humira PBS codes 9661L, 9678J)

Add an administrative note encouraging biosimilar prescribing for treatment naïve patients:

Note

Biosimilar prescribing policy

Prescribing of the biosimilar brand HYRIMOZ is encouraged for treatment naïve patients.

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

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

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.