5.01 ADALIMUMAB, 40 mg/0.4 mL pre-filled syringes, 40 mg/0.4 mL pen (cartridge) Humira®, Abbvie®

1 Purpose of application

1.1 The submission requested an Authority Required, General Schedule and Section 100 (Highly Specialised Drugs Program) listing for adalimumab 40 mg/0.4 mL for all currently PBS listed adalimumab indications.

1.2 The proposed new formulation of 40 mg/0.4 mL is a higher concentration of adalimumab which will replace the currently listed formulation (40 mg/0.8 mL). The new formulation retains the same dose of the active ingredient, adalimumab, and has also reduced and removed specific excipients. Table 1 presents the specific differences between the two formulations in terms of excipients.

Table 1: Current and proposed adalimumab formulation details

Currently listed formulation (0.4mg/0.8mL)	Proposed higher concentration formulation (0.4mg/0.4mL)
• Mannitol • Polysorbate 80 • Water for injection • Citric acid monohydrate • Sodium citrate • Monobasic sodium phosphate dehydrate • Dibasic sodium phosphate dehydrate • Sodium chloride	• Mannitol • Polysorbate 80 • Water for injection

Source: Table 1.1, p 9 of the submission. mg = milligram; mL = millilitre

1.3 Table 2 presents key components of the clinical issue addressed by the submission.

Table 2: Key components of the clinical issue addressed by the submission

Component	Description
Population	All adult and juvenile indications for which adalimumab 40mg/0.8mL is currently PBS-listed, which include: severe Crohn's disease, moderate to severe ulcerative colitis, severe active juvenile idiopathic arthritis, complex refractory fistulising Crohn's disease, severe active rheumatoid arthritis, severe psoriatic arthritis, active ankylosing spondylitis, severe chronic plaque psoriasis, and moderate to severe hidradenitis suppurativa.
Intervention	Adalimumab 40 mg/0.4 mL with or without methotrexate
Comparator	Adalimumab 40 mg/0.8 mL with or without methotrexate
Outcomes	DAS28-CRP; ACR response; HAQ-DI and SF36 at weeks 12 and 24; injection related pain assessment module (0-cm VAS) immediately after injection
Clinical claim	Adalimumab 40 mg/0.4 mL is equivalent in terms of comparative effectiveness and equivalent in terms of comparative safety to adalimumab 40 mg/0.8 mL. The trial included as the main evidence base of the submission (Trial M13-390) indicated that "Efficacy was assessed based on the pharmacodynamic variables", and thus no equivalence or non-inferiority margins were reported. In addition, the proposed formulation reduces pain on injection. The strength of the evidence regarding reduction of pain on injection is debatable, but the submission did not request any price premium over the currently listed formulation, which is appropriate.

Source: Table 1.2, p9 of the submission. ACR = American College of Rheumatology; cm = centimetre; DAS-28 = disease activity score; HAQ-DI = health assessment questionnaire –disability index; mg = milligram; mL = millilitre; PBS = Pharmaceutical Benefit's Scheme; SF36 = short form 36; VAS = visual analogue scale;

2 Requested listing

2.1 The requested restrictions for adalimumab 40 mg/0.4 mL are identical to those of the 40 mg/0.8 mL presentation.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 The submission was made under the TGA/PBAC Parallel process. The product was listed on the ARTG on 16 November 2017.

4 Population and disease

4.1 The submission sought listing of the 40 mg/0.4 mL formulation for all currently PBS listed indications of adalimumab 40 mg/0.8 mL. These include: severe Crohn's disease; moderate to severe ulcerative colitis; severe active juvenile idiopathic arthritis; complex refractory fistulising Crohn's disease; severe active rheumatoid arthritis; severe psoriatic arthritis; active ankylosing spondylitis; severe chronic plaque psoriasis; and moderate to severe hidradenitis suppurativa.

4.2 The submission did not provide evidence of clinical need for a higher concentration formulation of adalimumab.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated adalimumab 40 mg/0.8 mL as the comparator. As this is the same active ingredient and the same dose of active ingredient with the only difference being the concentration, and the removal of certain excipients, this is reasonable.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission is based on three randomised trials of adalimumab 40 mg/0.4 mL versus adalimumab 40 mg/0.8 mL in patients with rheumatoid arthritis (RA):

- M13-390 (n=100), a double blind, 24 week trial (the submission considered M13-390 and its open extension study (M13-692) to be the same trial) and;
- M12-783 (n=62) and M11-964 (n=60), two short term cross over single blind trials.

6.4 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
M11-964	A Multicenter, Randomized, Single-Blind Crossover Study of the Safety and Tolerability of Two Adalimumab Formulations in Adult Subjects with Rheumatoid Arthritis.	24 April 2013
M12-783	Multicenter, Randomized, Single-Blind Crossover Study of the Safety and Tolerability of Two Adalimumab Formulations in Adult Subjects with Rheumatoid Arthritis.	17 May 2013.
M13-390	Study to Assess Pharmacokinetic, Pharmacodynamic, Safety and Immunogenicity of a New Adalimumab Formulation in Subjects with Active Rheumatoid Arthritis.	21 Nov 2014
M13-692	A Phase 2b, Multicenter, Open-Label Study in Rheumatoid Arthritis Subjects Who Completed Preceding Study M13-390 with Adalimumab.	21 Nov 2014
Meta-analyses of direct randomised trials		
Pooled analysis of M12-783 & M11-964	Nash P, Vanhoof J, Hall S, Arulmani U, Tarzynski-Potempa R, Unnebrink K, Payne AN, Alfred Cividino Randomized crossover comparison of injection site pain with 40 mg/0.4 or 0.8mL formulations of adalimumab in patients with rheumatoid arthritis	Rheum Ther; 2016; 3: 257-498 (abstract)
	Nash, P., Vanhoof, J., Hall, S., Tarzynski-Potempa, R., Unnebrink, K. & Cividino, A. 2016b. A randomized crossover comparison of injection site pain with 40 mg/0.8 mL and 40 mg/0.4 mL formulations of adalimumab in patients with rheumatoid arthritis	Annals of Rheum Dis 2016; 75: 4970498 (abstract)

Source: Table 2.4, p31 of the submission.

6.5 The key features of the direct randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence, adalimumab 40mg/0.4mL versus 40mg/0.8mL

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes
M13-390	100	R, DB 24 weeks	Low	RA	ACR; DAS28-CRP; HAQ-DI; SF-36; injection site related pain; PK/immunogenicity; PD; safety
M12-783	62	R, SB 70 days after study drug stopped	Unclear		Immediate pain of injection on a VAS; safety
M11-964	60				

Source: compiled during the evaluation
DB=double blind; PD=pharmacodynamics; PK=pharmacokinetics R=randomised; RA=rheumatoid arthritis; SB=single blind

6.6 Though no evidence was presented for other indications outside of rheumatoid arthritis, the TGA evaluator considered that the development program was appropriate for the development of a new, higher concentration formulation of an existing strength (40 mg) of adalimumab for all approved adalimumab indications (p20 of CER).

Comparative effectiveness

6.7 The TGA evaluator concluded that the efficacy of the higher concentration formulation can be considered comparable to the efficacy of the current formulation (p29 of CER) based on:

- comparable DAS28-CRP responses at Weeks 12 and 24 in Study M13-390;
- comparable mean change from baseline DAS28-CRP at Weeks 36 and 48 in Study M13-692 (open label extension to M13-390);

- similar HAQ-DI, ACR20/50/70/90/100 responses, and SF-36 in Studies M13-390 and M13-692; and
- simulations of a potential increase in exposure did not have clinically meaningful impact on DAS28-CRP.

Comparative harms

6.8 The TGA evaluator noted that all studies showed a reduction in injection site pain with the new formulation (p9, TGA Delegate's file note). However, the data used to support this were potentially unreliable given they were derived from the single (patient)-blind cross-over trials and the risk of bias in VAS injection site pain was potentially high.

Interpretation of clinical evidence

6.9 The first- and second- round evaluators considered the benefit risk profile to be acceptable (p32 and p36, respectively). The TGA delegate's file note considered that the new formulation demonstrated bioequivalence to the current formulation.

Economic analysis

6.10 Based on the claim of therapeutic equivalence, the submission conducted a cost minimisation analysis.

6.11 Adalimumab 40 mg/0.4 mL was considered equivalent to 40 mg/0.8 mL. The submission stated that the requested price of adalimumab 40 mg/0.4 mL was the same as that of 40 mg/0.8 mL, and no cost offsets were assessed.

6.12 The submission stated that, as at 1 June 2017, the dispensed price for maximum quantity for a 2 pack, 4 pack and 6 pack pre-filled syringe or pen (cartridge) is $1,401.30, $2,709.24 and $3,987.46 respectively. The submission noted that the 4 pack was not listed on 1 June; the DPMQ for the 4 pack was obtained from the Schedule of Pharmaceutical Benefits, Summary of Changes effective 1 July 2017.

6.13 The submission's cost-minimisation analysis was reasonable.

Estimated PBS usage & financial implications

6.14 This submission was not considered by DUSC. The submission took a market share approach to estimate use and financial impact of listing the higher concentration formulation of adalimumab.

6.15 The submission considered that the estimated financial implications for the health budget of adalimumab 40 mg/0.4 mL were nil because the proposed medicine was expected to replace the currently PBS-listed adalimumab 40 mg/0.8 mL, the prices were identical and no additional costs or cost offsets are expected. This was reasonable.

6.16 It was possible that perceived benefits in the higher concentration concerning injection site pain could attract patients who would otherwise been treated with agents other than adalimumab in some indications. However, this is likely to be a small number.

6.17 The submission based its estimates on PBS item reports from Medicare Statistics for total services of all PBS-listed item numbers for adalimumab 40 mg/0.8 mL. Total sales of adalimumab were projected for six future years of listing using a logarithmic trend line. An uptake rate of 50% in the first full year of listing (2018) was assumed followed by a 100% uptake rate in the following year. As the costs associated with each formulation are identical, alternate assumptions on uptake rates and use projections had no effect on financial estimates.

6.18 Although not a matter for the PBAC, as the TGA determined that the new formulation is bioequivalent to the existing formulation, the PBS listing of high concentration product would move adalimumab into the F2 formulary and would trigger a statutory price reduction under s99ACB of the National Health Act 1953. This has the potential to result in the loss of some of the savings to Government that would have occurred under Section 5 of the 2017 Strategic Agreement between the Commonwealth and Medicines Australia.

7 PBAC Outcome

7.1 The PBAC recommended the listing of adalimumab injection (40 mg/0.4 mL) with the same restrictions as the currently listed forms of adalimumab 40 mg/0.8 mL on a cost-minimisation basis.

7.2 In making this recommendation, the PBAC noted that although the application for a higher concentration form of adalimumab met the requirements for a positive PBAC recommendation, the evidence that there is a clinical need for this formulation was not convincing, and there is potential for this listing to result in a considerable loss of savings to government. The PBAC considered that the Minister may wish to take these matters into account in progressing with this listing, and may wish to seek further advice from the Department on any other implications of the listing, particularly in relation to the terms of the Strategic Agreement between the Commonwealth and Medicines Australia.

7.3 The PBAC considered that adalimumab 40 mg/0.4 mL should be considered equivalent for the purposes of substitute (i.e. ‘a’ flagged in the schedule) with adalimumab 40 mg/0.8 mL.

7.4 The PBAC noted that the sponsor intends to delist the existing 40 mg/0.8 mL strength from the PBS upon listing of the 40 mg/0.4mL strength. The PBAC had no objection to the deletion, but noted that there should be no gap in access to subsidised adalimumab.

7.5 Consistent with the existing arrangements, the PBAC advised that adalimumab is not suitable for prescribing by nurse practitioners.

7.6 The PBAC has previously considered that adalimumab should not be exempt from the early supply rule.

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

Outcome:

Recommended

8 Recommended listing

Add new item:

Adalimumab (Humira®) 40 mg/0.4 mL pre-filled syringe and cartridge with same restrictions as 40 mg/0.8 mL formulations.

Delete item:

Delete adalimumab (Humira®) 40 mg/0.8 mL pre-filled syringe and cartridge.

9 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.

10 Sponsor's Comment

AbbVie welcomes the PBAC recommendation for the PBS listing of Humira 40mg/0.4mL