

**5.07 INFLIXIMAB (biosimilar),
100 mg injection, 1 vial,
Renflexis®,
Merck Sharp & Dohme (Australia) Pty Ltd.**

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drugs Program, Public and Private Hospital) listing of Renflexis®, or SB2, a biosimilar with the same indications and restrictions as the currently PBS listed brand of Remicade® (infliximab). Remicade is currently PBS listed for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis and Crohn's disease.

2 Requested listing

- 2.1 The requested listings are summarised below. Renflexis is marketed in some countries (including in the European Union) under the trade name Flixabi®.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer
INFLIXIMAB PBS Item Codes 10196P, 5753T, 5754W, 5755X, 5756Y, 5757B, 5758C, 9654D Powder for injection 100mg, 1 vial	1	0	\$ [REDACTED]	Renflexis® Merck Sharp & Dohme (Australia) Pty Ltd

Section 100 – Highly Specialised Drugs Program – Public: Moderate to severe ulcerative colitis, active ankylosing spondylitis, severe Crohn's disease, moderate to severe Crohn's disease, severe active psoriatic arthritis, severe active rheumatoid arthritis, severe chronic plaque psoriasis, complex refractory fistulising Crohn's disease.

INFLIXIMAB PBS Item Codes 10184B, 6448J, 9613Y, 9612X, 6496X, 6397Q, 9617E, 9674E Powder for injection 100mg, 1 vial	1	0	\$ [REDACTED]	Renflexis® Merck Sharp & Dohme (Australia) Pty Ltd
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Section 100 – Highly Specialised Drugs Program – Private: Moderate to severe ulcerative colitis, active ankylosing spondylitis, severe Crohn's disease, moderate to severe Crohn's disease, severe active psoriatic arthritis, severe active rheumatoid arthritis, severe chronic plaque psoriasis, complex refractory fistulising Crohn's disease.

INFLIXIMAB, PBS Item Code 10057H Powder for injection 100mg, 1 vial	1	1	\$ [REDACTED]	Renflexis® Merck Sharp & Dohme (Australia) Pty Ltd
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Section 100 – Highly Specialised Drugs Program – Private: Acute severe ulcerative colitis

INFLIXIMAB PBS Item Code 10067W				Renflexis® Merck Sharp & Dohme (Australia)
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Public Summary Document – November 2016 PBAC Meeting

Powder for injection 100mg, 1 vial 5 1 \$ [REDACTED] Pty Ltd

Section 100 – Highly Specialised Drugs Program – Public: Acute severe ulcerative colitis

INFLIXIMAB Renflexis® Merck Sharp &
PBS Item Code Dohme
4284L (Australia)
Powder for injection 100mg, 1 vial 1 2 \$ [REDACTED] Pty Ltd

Repatriation Pharmaceutical Benefits – War-caused or service-related disability of refractory rheumatoid arthritis

*all Dispensed Price for Maximum Quantity (DPMQ) was based on the price reported in the submission. The DPMQ for Remicade has been increased slightly since 1st July 2016 due to indexation.

- 2.2 The submission sought the listing of Renflexis on a cost minimisation basis compared with Remicade.

3 Background

TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the second round TGA Clinical Evaluation Report (CER), Delegate’s Request for ACPM Advice and ACPM outcome were available. The ACPM considered Renflexis to have an overall positive benefit-risk profile for all indications Remicade is registered for, and advised that it considered Renflexis a biosimilar of Remicade.

- 3.1 This was the first consideration of Renflexis by the PBAC.

- 3.2 At its July 2015 meeting, the PBAC recommended the listing of the first biosimilar infliximab (Inflectra®) as a biosimilar of Remicade, where the equi-effective doses were 100 mg infliximab Inflectra and 100 mg Remicade. The PBAC recommended that the same indications that apply to Remicade should apply to Inflectra. The PBAC also recommended that Inflectra brand of infliximab should be treated as a schedule equivalent (‘a’ flagged) to the Remicade brand of infliximab.

Substitution of biosimilars at the pharmacist level (‘a’ flagging)

- 3.3 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. 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.
- 3.4 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.

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

Extract from the Explanatory Notes to the PBS Schedule^a

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.

- 3.6 At the March 2015 meeting, the PBAC:

“indicated it would consider the marking of equivalent (i.e. ‘a’ flagging) in the Schedule of Pharmaceutical Benefits (the Schedule) of biosimilar medicines with their reference medicine on a case by case basis, taking into account the evidence presented in each submission to list a biosimilar medicine.”

- 3.7 When ‘a’ flagging of biosimilar brands and their reference brands was discussed by the PBAC at its special meeting on 17 April 2015, the PBAC advised that biosimilar products would be recommended for ‘a’ flagging, “where the data are supportive of this conclusion.”

“The PBAC advised that the following would be relevant considerations in establishing that a biosimilar product could be ‘a’ flagged with the originator product:

- Absence of data to suggest significant differences in clinical effectiveness or safety compared with the originator product;
- Absence of identified populations where the risks of using the biosimilar product are disproportionately high;
- Availability of data to support switching between the originator product and the biosimilar product;
- Availability of data for treatment-naïve patients initiating on the biosimilar product;
- Whether the Therapeutic Goods Administration has deemed a product to be biosimilar with the originator product.

The PBAC considered that where a biosimilar product could not be ‘a’ flagged at the time of PBS listing, data should be collected to support ‘a’ flagging at a later point.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

4 Clinical place for the proposed therapy

^a Symbols used in the Schedule - <http://www.pbs.gov.au/info/healthpro/explanatory-notes/section2/section-2-symbols>

- 4.1 Infliximab (Remicade) is currently listed on the PBS for the following conditions:
- acute severe ulcerative colitis
 - moderate to severe ulcerative colitis
 - severe Crohn's disease
 - moderate to severe Crohn's disease (paediatric patients)
 - complex refractory fistulising Crohn's disease
 - severe active rheumatoid arthritis
 - active ankylosing spondylitis
 - severe active psoriatic arthritis
 - war-caused or service-related disability of refractory rheumatoid arthritis
 - severe chronic plaque psoriasis
- 4.2 The submission claimed an identical place for Renflexis in the clinical management algorithm to Remicade. As Renflexis is expected to be used exactly the same way as Remicade, its listing would not affect treatment patterns or co-administered medicines.

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

5 Comparator

- 5.1 The submission nominated Remicade as the comparator. The PBAC considered that this was appropriate. The other infliximab brand listed on the PBS (Inflectra) is also a potential comparator.

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

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 was based on one head-to-head trial (Trial SB2-G31-RA) comparing Renflexis (co-administered with methotrexate) to Remicade (co-administered with methotrexate) in patients with moderate to severe rheumatoid arthritis who have had an inadequate response to methotrexate therapy (N=584). The study duration for the main period of the trial was 54 weeks. Trial SB2-G31-RA included a transition-extension study (switching study) from week 54, where subjects originally assigned to Remicade (N=195) were re-randomised to either continue to receive Remicade (N=101) or to switch to Renflexis (N=94). Subjects originally assigned to

Renflexis (N=201) were sham randomised (to preserve blinding) and continued to receive Renflexis. The switching study was conducted until week 78 (for a duration of 24 weeks). Of the 396 patients entering the transition-extension study, 370 patients (93.4%) completed week 78. Efficacy and safety data for this switching study were not provided with the submission, however, a summary of the results at week 78 became available during the evaluation in the CER.

6.4 Details of the trial presented in the submission are provided in table 1.

Table 1: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Trial SB2-G31-RA	30-week Clinical Study Report Protocol: A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to INF in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy.	10 February 2015
	54-week Clinical Study Report Protocol: A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to INF in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy.	7 July 2015
	Choe, J.-Y.; Prodanovic, N.; Niebrzydowski, J.; Staykov, I.; Dokoupilova, E.; et al. A randomised, double-blind, phase III study comparing SB2, an Infliximab biosimilar, to the infliximab reference product (INF) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy.	Annals of the Rheumatic Diseases 2015; 74 (Suppl. 2): 706-707.
	ClinicalTrials.gov: NCT01936181 A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to INF in Subjects With Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy	30 November 2015

INF = infliximab reference product

Source: Table B.2-2, p29 of the submission.

6.5 The key features of the direct randomised trial are summarised in table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Renflexis vs. Remicade					
Trial SB2-G31-RA	584	R, DB 78 weeks*	Low	RA patients who have failed methotrexate	ACR20 response rate ACR50 response rate ACR70 response rate

DB=double blind; R=randomised; RA = rheumatoid arthritis; ACR = American College of Rheumatology

* **Main study/period:** Subjects were randomised in a 1:1 ratio to receive either SB2 3 mg/kg or INF (Remicade) 3 mg/kg via a 2 hour intravenous infusion at Weeks 0, 2 and 6 and then every 8 weeks until Week 46. There were 54 weeks of active treatment (the expected study duration per individual subject was 54 weeks after randomisation). The primary outcome of ACR20 response rate, defined as at least a 20% improvement in the core set measures for a patient to reach improvement, was assessed at Week 30. From Week 30, the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's rheumatoid arthritis (RA) symptoms were not well controlled by the existing dose. If adequate response was achieved, subjects were continued on the selected dose.

Transition-extension study/period: At Week 54, subjects receiving INF (Remicade) were randomised in a 1:1 ratio to either continue to receive INF (Remicade) or to be transitioned to SB2. Subjects receiving SB2 from the main study continued to receive extended treatment of SB2 up to Week 70. This study period consisted of 24 weeks of active treatment (subjects were enrolled in the transition-extension period for up to 24 weeks after Week 54 of the main study), conducted from week 54 to week 78. Subjects received SB2 or INF (Remicade) from 3 to 7.5 mg/kg every 8 weeks at Weeks 54, 62 and 70 via IV infusion for 2 hours.

Source: compiled during the evaluation

- 6.6 The measures undertaken by investigators to minimise bias in the double blind portion of trial SB2-G31-RA appeared reasonable and the overall risk of bias for the trial is considered to be low.
- 6.7 A pre-specified 2-sided equivalence margin of 15 percentage points in the proportion of patients achieving and American College of Rheumatology (ACR) 20 per cent improvement criteria (ACR20) was used in the submission to assess equivalence between Renflexis and Remicade. An equivalence margin of 15 percentage points was also nominated in the Inflectra submission, however as the 95% CI did not approach 15% in that submission, the PBAC did not explicitly indicate if this margin was acceptable (Infliximab (biosimilar) Inflectra®, PSD, July 2015 PBAC meeting, p12.).
- 6.8 No longer term effectiveness and safety data beyond the duration of the transition-extension study (78 weeks) of Renflexis and Remicade were available.
- 6.9 The submission did not provide evidence of the effectiveness and safety of Renflexis compared with Remicade in patients with indications other than rheumatoid arthritis.

Comparative effectiveness

- 6.10 The trial results for the ACR20 (primary outcome) in the Full Analysis Set (FAS^b) and Per Protocol Set 1 (PPS1^c), ACR50 and ACR70 in the FAS at week 30 are summarised in table 3.

^b All randomised subjects who received at least one dose of SB2 or Remicade. Subjects were analysed according to the treatment they were assigned at randomisation. However, subjects who did not qualify for randomisation and were inadvertently randomised into the study were excluded from the FAS, provided these subjects did not receive any investigational product during that study phase.

^c All FAS subjects who completed the week 30 visit and had an adherence (from baseline to week 30) within the range of 80–120% for both the expected number of investigational product administrations and the expected sum of methotrexate doses without any major protocol deviations (PD) that affected the efficacy assessment. Major PDs that led to exclusion

Table 3: Results of ACR20, ACR50 and ACR70 response at week 30 in Trial SB2-G31-RA

Outcome	Renflexis n/N (%)	Remicade n/N (%)	Adjusted difference ^a 95% CI
ACR20			
FAS ^b	161/290 (55.5%)	173/293 (59.0%)	-3.0% (-10.9%, 5.0%)
PPS1	148/231 (64.1%)	163/247 (66.0%)	-1.9% (-10.3%, 6.5%)
ACR50			
FAS ^b	89/290 (30.7%)	99/293 (33.8%)	-2.5% (-10.1%, 5.0%)
ACR70			
FAS ^b	45/290 (15.5%)	50/293 (17.1%)	-1.1% (-7.1%, 4.9%)

ACR = American College of Rheumatology; CI = confidence interval; FAS = full analysis set; PPS1 = per protocol set 1

^aThe adjusted treatment difference and its 95% CI were analysed by a non-parametric method using NParCov with baseline C-reactive protein (CRP) as a covariate, and stratified by region. Adjusted difference and CI results have been rounded to one decimal place for consistency.

^b Subjects with missing ACR20, ACR50 or ACR70 response at week 30 were considered as non-responders at week 30.

Source: modified from Table B.6-1, p39 of the submission; Trial SB2-G31-RA 54-week CSR, Table 11-5, p78; modified from Table B.6-2, p41 of the submission; Trial SB2-G31-RA 54-week CSR, Table 11-9, p82; Trial SB2-G31-RA 54-week CSR, Table 11-11, p83

- 6.11 The trial results for the ACR20, ACR50 and ACR70 response at week 54 in the FAS are summarised in table 4.

Table 4: Results of ACR20, ACR50 and ACR70 response at week 54 in Trial SB2-G31-RA

Outcome	Renflexis n/N (%)	Remicade n/N (%)	Adjusted difference ^a 95% CI
ACR20			
FAS ^b	147/290 (50.7%)	154/293 (52.6%)	-1.2% (-9.2%, 6.9%)
ACR50			
FAS ^b	93/290 (32.1%)	87/293 (29.7%)	3.1% (-4.3%, 10.4%)
ACR70			
FAS ^b	53/290 (18.3%)	52/293 (17.7%)	1.1% (-5.1%, 7.3%)

ACR = American College of Rheumatology; CI = confidence interval; FAS = full analysis set

^aThe adjusted treatment difference and its 95% CI were analysed by a non-parametric method using NParCov with baseline C-reactive protein (CRP) as a covariate, and stratified by region. Adjusted difference and CI results have been rounded to one decimal place for consistency.

^b Subjects with missing ACR20, ACR50 or ACR70 response at week 54 were considered as non-responders at week 54.

Source: modified from Table B.6-3, p43 of the submission; Trial SB2-G31-RA 54-week CSR, Table 11-7, p81, Table 11-10, p82; Trial SB2-G31-RA 54-week CSR, Table 11-8, p81, Table 11-11, p83

- 6.12 At both Week 30 and Week 54, the proportions of patients achieving ACR20, ACR50 or ACR70 were similar in patients treated with either Renflexis or Remicade. The 95% confidence interval for the adjusted difference in treatment effect at both week 30 and week 54 between the groups was contained within the pre-specified 15% equivalence margin.
- 6.13 The trial results for the ACR20, ACR50 and ACR70 response during the transition-extension period (weeks 54 to 78) are summarised in table 5.

from this set were pre-specified prior to unblinding the treatment codes for analyses.

Table 5 ACR20, ACR50 and ACR70 response rates by visit from week 54 to week 78

ACR response	Timepoint	Treatment group					
		Renflexis -> Renflexis		Remicade -> Renflexis		Remicade -> Remicade	
		n/N	%	n/N	%	n/N	%
ACR20	Week 54	132/201	65.7%	67/94	71.3%	70/101	69.3%
	Week 62	129/193	66.8%	68/94	72.3%	67/101	66.3%
	Week 70	118/180	65.6%	61/88	69.3%	68/98	69.4%
	Week 78	123/180	68.3%	54/85	63.5%	64/93	68.8%
ACR50	Week 54	87/201	43.3%	39/94	41.5%	40/101	39.6%
	Week 62	79/193	40.9%	42/94	44.7%	42/101	41.6%
	Week 70	78/180	43.3%	36/88	40.9%	43/98	43.9%
	Week 78	73/180	40.6%	32/85	37.6%	44/93	47.3%
ACR70	Week 54	49/201	24.4%	25/94	26.6%	23/101	22.8%
	Week 62	41/193	21.2%	22/94	23.4%	21/101	20.8%
	Week 70	46/180	25.6%	18/88	20.5%	25/98	25.5%
	Week 78	46/180	25.6%	19/85	22.4%	29/93	31.2%

ACR = American College of Rheumatology; N = number of patients; n = number of responders
 Source: Trial SB2-G31-RA 78-week CSR, Table 12-5, pp 126-127

- 6.14 The PBAC considered that as the transition period was an extension of the clinical trial evaluated as part of the submission, the attributes of the extension study would be similar to those identified as part of the clinical study. The PBAC noted that the mean ACR20, ACR50 and ACR70 responses at weeks 62, 70 and 78 were comparable across all groups.

Comparative harms

- 6.15 The treatment emergent adverse events (TEAEs), including serious TEAEs (SAEs), reported in each arm of the trial at week 30 and week 54 are summarised in table 6.

Table 6: Summary of treatment-emergent adverse events at week 30 and week 54 in Trial SB2-G31-RA (Safety Set)

Category ^a	Renflexis N=290 n (%)	Remicade N=293 n (%)
Week 30		
TEAEs	167 (57.6%)	170 (58.0%)
Study drug-related TEAEs	62 (21.4%)	59 (20.1%)
Serious TEAEs (SAEs)	26 (9.0%)	26 (8.9%)
Study drug-related SAEs	10 (3.4%)	5 (1.7%)
TEAEs of special interest ^b	9 (3.1%)	6 (2.0%)
TEAEs leading to study drug discontinuation	30 (10.3%)	16 (5.5%)
TEAEs associated with an infusion-related reaction	15 (5.2%)	13 (4.4%)
Deaths	0 (0.0%)	1 (0.3%)
Week 54		
TEAEs	179 (61.7%)	191 (65.2%)
Study drug-related TEAEs	70 (24.1%)	69 (23.5%)
Serious TEAEs (SAEs)	29 (10.0%)	31 (10.6%)

Study drug-related SAEs	10 (3.4%)	7 (2.4%)
TEAEs of special interest ^b	9 (3.1%)	7 (2.4%)
TEAEs leading to study drug discontinuation	30 (10.3%)	24 (8.2%)
TEAEs associated with an infusion-related reaction	17 (5.9%)	15 (5.1%)
Deaths	0 (0.0%)	1 (0.3%)

TEAE = treatment-emergent adverse event; SAE = serious treatment-emergent adverse event

^a For each row category, a subject with 2 or more adverse events in that category is counted only once.

^b Serious infection or tuberculosis

Source: modified from Tables B.6-4 and B.6-5, p46 of the submission; Trial SB2-G31-RA 30-week CSR, Table 12-2, p91; Trial SB2-G31-RA 54-week CSR, Table 12-3, p98

- 6.16 At week 30, there was a numerically higher incidence of study drug-related serious treatment-emergent adverse events in the Renflexis arm compared with the Remicade arm. These results were equivalent at week 54.
- 6.17 A summary of TEAEs, SAEs and TEAEs of special interest at week 78 is presented in table 7.

Table 7: Summary of TEAEs at week 78 in Trial SB2-G31-RA (Ex-SAF)

Category	Treatment Group		
	Renflexis -> Renflexis N=201 n (%)	Remicade -> Renflexis N=94 n (%)	Remicade -> Remicade N=101 n (%)
Week 78			
TEAEs	81 (40.3%)	34 (36.2%)	36 (35.6%)
Study drug-related TEAEs	28 (13.9%)	13 (13.8%)	13 (12.9%)
Serious TEAEs (SAEs)	7 (3.5%)	6 (6.4%)	3 (3.0%)
Study drug-related SAEs	2 (1.0%)	4 (4.3%)	2 (2.0%)
TEAEs of special interest ^a	1 (0.5%)	2 (2.1%)	1 (1.0%)
TEAEs leading to study drug discontinuation	3 (1.5%)	3 (3.2%)	3 (3.0%)
TEAEs associated with an infusion-related reaction	7 (3.5%)	3 (3.2%)	2 (2.0%)

Ex-SAF = Extended Safety Set; TEAE = treatment-emergent adverse event; SAE = serious treatment-emergent adverse event

^a Serious infection or tuberculosis (TB)

Source: Trial SB2-G31-RA 78-week CSR, Table 12-5, pp126-127

- 6.18 There was a numerically higher rate of TEAEs for patients who continued on Renflexis, compared to patients in the Remicade/Remicade and Remicade/Renflexis treatment groups at week 78. There were no substantial differences in TEAEs between the Remicade/Remicade and Remicade/Renflexis groups.
- 6.19 The proportion of patients (in the extended safety set) who had at least one positive anti-drug antibodies (ADA) result at week 78 was 53.6% in the Renflexis/Renflexis group, 50.5% in the Remicade/Remicade group, and 45.7% in the Remicade/Renflexis group. There were numerical differences between treatment groups at baseline (week 54) in the prevalence of ADA (60.7% for the Renflexis/Renflexis group, 53.5% for the Remicade/Remicade group, and 56.4% for the Remicade/Renflexis group). The 78 week CSR stated (p182) that the differences

in ADA at week 78 may have been related to the differences in ADA at week 54. The PBAC noted that the ACPM considered that while ADAs were slightly higher in the Renflexis group, it did not appear to have a significant impact on efficacy or safety.

- 6.20 There was no further evidence in the transition-extension trial to suggest differences in the efficacy, safety and immunogenicity of Remicade, Renflexis, or switching from Remicade to Renflexis. However, this was in the context of small sample sizes in the transition-extension period that may not have been powered to detect differences in these outcomes.

Clinical claim

- 6.21 The submission described Renflexis as equivalent in terms of comparative effectiveness and comparable in terms of comparative safety over Remicade. The PBAC considered that the submission's claim was reasonable for patients with moderate to severe rheumatoid arthritis, supported by the evidence from trial SB2-G31-RA.
- 6.22 . The PBAC noted the ACPM advice that declared Renflexis as a biosimilar of Remicade and was satisfied to extrapolate the results of the rheumatoid arthritis trial to all indications, including the inflammatory bowel disease indications.
- 6.23 No longer term effectiveness and safety data of Renflexis compared with Remicade (beyond the 78 week duration of the transition-extension study) was available. The TGA CER (p29) stated:
"No unique risks have been identified [of SB2] compared with Remicade. Risks related to loss of efficacy, new safety signals and immunogenicity may emerge with long-term use in larger patient numbers."
- 6.24 Efficacy and safety data for the switching study of trial SB2-G31-RA were not provided with the submission. However, a summary of the results became available during the evaluation in the TGA CER (per 6.1 above). The TGA CER (pp29-30) stated:
"The risks associated with switching between SB2, Remicade and other biosimilars are largely unknown. They should be assessed with analysis of transition-extension data in Trial SB2-G31-RA and by appropriate post-marketing pharmacovigilance".
- 6.25 The current PBS listing of Remicade requires that prescribers are specialists in the therapeutic area for which infliximab is being prescribed. Therefore, should Renflexis be 'a' flagged, the decision to permit switching at the point of prescribing is made by an appropriate specialist.
- 6.26 The submission did not discuss any relevant comparative evidence on pharmacokinetics. Pharmacokinetic data from trial SB2-G31-RA in patients with rheumatoid arthritis, and from the Shin et al. study in healthy patients, were not presented in the submission. However TGA was satisfied that these pharmacokinetic studies demonstrated similarity between Renflexis and Remicade for the pharmacokinetic parameters tested (TGA CER, pp14-15).

6.27 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.28 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.29 The submission presented a cost-minimisation analysis. Consistent with the clinical evidence presented, the submission proposed an equi-effective dose of: 100 mg Renflexis = 100 mg Remicade. No other costs were considered as administration of Renflexis and Remicade is identical in terms of both number of administrations and method of administration, and no differences in adverse events are expected. The PBAC considered that this was appropriate.

Drug cost/patient/cycle: \$██████/patient/cycle for rheumatoid arthritis

6.30 Renflexis has an average cost of \$██████/patient/cycle is based on an average dose of 3mg/kg every 8 week cycle for patients with rheumatoid arthritis. The average patient weight was assumed to be the same as that in trial SB2-G31-RA (72.1kg – requiring 216mg/dose). The average number of vials required per dose was rounded up to 2.5 vials, to allow for wastage. The average cost per vial was based on a weighted price of \$██████/vial, assuming 70% public hospital use as per the current PBS listings for infliximab in 2015. There is a greater frequency of treatment during initiation where patients will receive this dose (3mg/kg) at weeks 0, 2 and 6.

6.31 The cost per patient per cycle for other PBS indications cannot be reliably estimated, given the lack of data on average patient body weight. However, for any requested indication, the drug cost/patient/cycle for Renflexis is expected to be the same as that for Remicade, given that the requested price and dosage of Renflexis are the same as that of Remicade.

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC. The submission used a market share approach to estimate the extent of use and costs in the first five years of listing. The listing of Renflexis is not expected to increase the numbers of patients that would be treated with infliximab across the proposed period or increase the cost to the R/PBS.

Table 8: Estimated use and financial implications

	2017 Year 1	2018 Year 2	2019 Year 3	2020 Year 4	2021 Year 5
Estimated extent of use					
Number treated	██████	██████	██████	██████	██████
Market share	█%	█%	█%	█%	█%
Scripts	██████	██████	██████	██████	██████
Estimated net cost to PBS/RPBS/MBS	\$0	\$0	\$0	\$0	\$0

Source: Table E.3-1, p58 of the submission.

The redacted table above shows that at year 5, the estimated number of patients would be 50,000 – 100,000.

- 6.33 The PBAC did not expect the listing of Renflexis to result in additional cost to PBS/RPBS/MBS as Renflexis has requested the same price as that of Remicade with the doses and route of administration being the same.

Quality Use of Medicines

- 6.34 The submission did not raise issues relating to the quality use of medicines. The TGA CER suggested that risks associated with switching should be assessed by appropriate post-marketing pharmacovigilance.

Financial Management – Risk Sharing Arrangements

- 6.35 The sponsor did not propose any risk sharing arrangements..

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of infliximab (Renflexis) as a biosimilar of infliximab (Remicade) on a cost minimisation basis with infliximab (Remicade). The equi-effective doses are 100 mg infliximab (Renflexis) and 100 mg infliximab (Remicade). The PBAC recommended that infliximab (Renflexis) be listed for all indications that are PBS listed for infliximab (Remicade):

- Acute severe ulcerative colitis
- Moderate to severe ulcerative colitis
- Severe refractory Crohn's disease
- Refractory Fistulating Crohn's disease
- Severe active rheumatoid arthritis
- Active ankylosing spondylitis
- Severe active psoriatic arthritis
- Severe chronic plaque psoriasis

- 7.2 The PBAC considered that a claim of non-inferior comparative effectiveness and non-inferior comparative safety was adequately supported. The PBAC noted that the ACPM was satisfied that the submitted data showed that Renflexis is similar to Remicade in terms of efficacy and safety, further noting that the ACPM had stated there were sufficient data to for it to be satisfied that Renflexis is a biosimilar of Remicade.

- 7.3 The Committee agreed that originator brand infliximab (Remicade) was the appropriate comparator.

- 7.4 The PBAC noted the ACPM advice in relation to extrapolation of indications, and was satisfied that the results of the SB2-G31-RA trial in rheumatoid arthritis could be extrapolated to all other indications for which Remicade is PBS listed, including the

inflammatory bowel disease indications (Crohn's disease and ulcerative colitis).

- 7.5 The PBAC advised the Minister that it considered the Remicade and Renflexis brands of infliximab could be marked as equivalent in the Schedule of Pharmaceutical Benefits ('a' flagged), for the purposes of substitution by the pharmacist at the point of dispensing for all indications. The PBAC noted that the substitution process allows for patient and prescriber choice and is not automatic. For any individual prescription, a prescriber may choose to not permit brand substitution. If, on the other hand, substitution has been permitted by the prescriber, the patient may choose which brand they wish to receive from the pharmacist.
- 7.6 In forming its view on brand substitution ('a' flagging), the PBAC considered a range of factors including:
- The key randomised clinical study in rheumatoid arthritis did not indicate differences in efficacy or safety of Renflexis compared with Remicade.
 - The clinical data provided in the submission did not suggest there were any identified populations where the risks of using the biosimilar product in place of the reference biologic were disproportionately high.
 - In the SB2-G31-RA transition-extension period which included 24 weeks of additional data, including a one-way switch from Remicade to Renflexis, the clinical evidence suggested no difference in efficacy, safety or immunogenicity between the biosimilar and the reference biologic. The proportion of patients who had at least one positive anti-drug antibodies result at week 78 was similar between for the Renflexis/Renflexis, Remicade/Remicade and Remicade/Renflexis groups.
 - The evidence presented in the SB2-G31-RA trial in treatment-naïve patients with rheumatoid arthritis initiating on either Remicade or Renflexis support a finding that Renflexis has equivalent effectiveness and equivalent safety compared to Remicade.
 - The ACPM has declared Renflexis a biosimilar for Remicade. The ACPM was satisfied of the similar safety and efficacy of Renflexis and Remicade in rheumatoid arthritis, and that this could be extrapolated to ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, refractory fistulating Crohn's disease and ulcerative colitis. The ACPM also noted that there was no evidence to suggest the presence of anti-drug antibodies affected either the efficacy or safety of infliximab.

The PBAC noted this submission sought listing of a second biosimilar brand of a biologic and that, in recommending an 'a' flag for Renflexis with Remicade, it is possible that switches between more than two brands of infliximab will occur in practice. The PBAC had no reason to consider this would affect patient outcomes.

- 7.7 The PBAC advised that Renflexis and all other brands of infliximab are not suitable for prescribing by nurse practitioners.
- 7.8 The PBAC recommended that the Early Supply Rule should not apply, as with other currently listed brands of infliximab.
- 7.9 The PBAC noted that this submission is not eligible for an Independent Review as it

received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item: Infliximab (Renflexis), 100 mg vial

Listings the same as for 100 mg infliximab (Remicade)

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

The sponsor had no comment.