

5.15 INFLIXIMAB (biosimilar) injection, 100mg, Inflectra[®], Hospira

1 Purpose of Application

- 1.1 To request a Section 100 (Highly Specialised Drugs Program) listing of Inflectra[™] (infliximab), a biosimilar (or similar biological medicinal product (SBMP)), 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.
- 1.2 The Minister (delegate) also requested the PBAC provide advice under section 101(3) of the *National Health Act 1953* (the Act) on the marking of Inflectra as equivalent (*i.e.* "a" flagging) to Remicade in the Schedule.

Note: Hospira advised the Department on 29 May 2015 that: "Whilst Hospira is amenable to 'a' flagging for biosimilar Infliximab, Hospira is not formally requesting 'a' flagging status for this minor PBAC submission for biosimilar infliximab, (Inflectra[™]) lodged in April 2015. In reference to TGA's current position not to endorse interchangeability of biosimilars in its "Evaluation of Biosimilar" guidelines, Hospira will not apply for 'a' flagging request for biosimilar infliximab application at this time but defer to the discretion of the PBAC to make judgment on interchangeability/substitution upon assessment of available evidence supplied."

2 Requested listing

- 2.1 Inflectra is marketed in some countries by Celltrion Inc. under the trade name "Remsima". Several documents refer to Inflectra as Remsima or CT-P13.
- 2.2 The proposed listings are for the same indications as Remicade with the statutory 16% price reduction in accordance with the *National Health Act 1953*.
- 2.3 In addition to the submission, the sponsor provided the following evidence:
 - TGA documents provided at the time of the lodgement of the submission
 - ACPM ratified resolution
 - Supplementary clinical section addressing the use of Inflectra in IBD conditions
 - A discussion of the data supportive of substitution at the point of dispensing
- 2.4 The sponsor claimed that the provided evidence, as well as demonstrating highly similar efficacy, safety and immunogenicity features in AS and RA patients who are infliximab-naïve, also displays, "consistently similar efficacy, safety and immunogenicity attributes following a single transition of Remicade[®] treated AS and RA patients on CT-P13 [Inflectra]".

3 Background

- 3.1 The following information is outlined below:
- Previous PBAC consideration of biosimilars
 - Substitution of biosimilars at the pharmacist level (“a” flagging)
 - TGA consideration of Inflectra

Previous PBAC consideration of biosimilars

- 3.2 Since the TGA has developed a biosimilars evaluation pathway, the PBAC has previously recommended the subsidy of biosimilars for epoetin alfa, filgrastim and insulin glargine.
- 3.3 Epoetin lambda was recommended for subsidy by the PBAC in July 2010. The PBAC noted that epoetin lambda had been approved by TGA under the Similar Biological Medicinal Product guidelines with the reference product epoetin alfa. However, the TGA registered the epoetin alfa biosimilar under a different Australian Biologic Name, epoetin lambda, due to differences in the glycosylation pattern of the product. The Minister subsequently declared epoetin lambda to be a different drug and both epoetin alfa and epoetin lambda remain on the PBS F1 formulary.

The PBAC has recommended three biosimilars to Neupogen® filgrastim. The TGA delegate proposed to list the first filgrastim biosimilar (Nivestim®) on the basis of comparable efficacy and safety and having the same non-proprietary name as its reference product. This was determined using an abridged dataset consistent with European Medicines Agency guidelines adopted by the TGA. At the time of listing the first filgrastim biosimilar (Nivestim®), the PBAC recommended that “a” flagging for the purposes of subsection 103(2A)(b) of the *National Health Act 1953* should not be applied to the reference and biosimilar filgrastim products, noting the absence of a TGA issued statement, at the time of consideration, that would support “a” flagging.

- 3.4 Subsequent biosimilars for filgrastim (TevaGrastim and Zarzio) were listed on the PBS under the same conditions as Nivestim®.
- 3.5 At the March 2015 meeting, the PBAC recommended the listing of the insulin glargine biosimilar Basaglar® on a cost minimisation basis with the reference product, Lantus. In response to a request from the Minister the PBAC provided advice regarding “a” flagging in the Schedule of Pharmaceutical Benefits of the two insulin glargine brands. This advice was not published in the March 2015 PBAC meeting positive recommendations document.

Substitution of biosimilars at the pharmacist level (“a” flagging)

- 3.6 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.

- 3.7 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.
- 3.8 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.

- 3.9 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.”
- 3.10 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.

^a [Symbols used in the Schedule](#) - accessed 27/05/2015

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.”

TGA consideration of Inflectra

- 3.11 Inflectra has been considered by the ACPM. The ACPM has stated there were sufficient data to declare Inflectra a biosimilar for Remicade and to extrapolate the conclusion of equivalent efficacy from the rheumatoid arthritis and ankylosing spondylitis indications for which evidence was provided to IBD conditions.
- 3.12 The ACPM noted “that there is insufficient evidence to discount the possibility that there are different rates of TB activation for this biosimilar product compared to the incidence with Remicade”, however the ACPM discussed some possible non-drug related causes for the difference. Monitoring for TB is recommended in the product information, and TB surveillance is included in the Risk Management Plan. The ACPM advised that, despite the observed differences, the findings are acceptable to conclude similarity with the safety profile of Remicade.

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

4 Clinical place for the proposed therapy

- 4.1 Infliximab (Remicade) is currently listed on the PBS for the following conditions:
- Acute severe ulcerative colitis
 - Moderate to severe ulcerative colitis
 - Severe refractory Crohn’s disease
 - Refractory fistulising Crohn’s disease
 - Severe active rheumatoid arthritis
 - Active ankylosing spondylitis
 - Severe active psoriatic arthritis
 - Severe chronic plaque psoriasis
- 4.2 The submission claimed an identical place in the clinical management algorithm to Remicade. As Inflectra is expected to be used exactly the same way as Remicade, the listing of Inflectra would not affect treatment patterns or co-administered medicines.

5 Comparator

- 5.1 The minor submission appropriately nominated Remicade as the comparator.

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments expressed concern around perceived differences in efficacy that may result from switching and substitution between the biosimilar and reference biologic.
- 6.3 The PBAC also acknowledged the numerous correspondences received, separate to the Consumer Comments facility, concerning the PBAC's position on the "a" flagging of biosimilars (as outlined at its April 2015 Special Meeting). The PBAC further noted the comments made by various patient and clinician groups at the PBAC hearing on biosimilar medicines particularly in relation to pharmacy level substitution.
- 6.4 This section addresses the following:
- Clinical trials provided to support the proposed listing
 - Comparative effectiveness in patients with rheumatoid arthritis
 - Comparative effectiveness in patients with ankylosing spondylitis
 - Pharmacokinetic analyses
 - Comparative effectiveness in patients with psoriatic arthritis
 - Comparative effectiveness in patients with psoriasis
 - Comparative effectiveness in patients with Crohn's disease and ulcerative colitis
 - Comparative Harms
 - Pharmacovigilance
 - Clinical Claim
 - Substitution between the biosimilar and the reference biologic

Clinical trials

- 6.5 The clinical evidence provided in the submission was based on three studies: (1) a randomised phase III study in patients with rheumatoid arthritis, Study CT-P13 3.1 (Study 3.1); (2) a randomised phase I pharmacokinetic study in patients with ankylosing spondylitis Study CT-P13 1.1 (Study 1.1); and (3) a small phase I pharmacokinetic study in patients with rheumatoid arthritis Study CT-P13 1.2 (Study 1.2). The publication details on these studies are given in Table 1.
- 6.6 In addition, the sponsor provided evidence relating to substitution of Remicade with Inflectra consisting of efficacy, safety and immunogenicity results from Study CT-P13 3.2 (extension of Study 3.1 in rheumatoid arthritis) and Study CT-P13 1.3 (extension of Study 1.1 in ankylosing spondylitis). Patients enrolled into the extension studies who were previously randomised to Remicade were switched to Inflectra.
- 6.7 A search of clinical trial registries found the following studies:
- NCT02452151 – a randomised phase IV study comparing Inflectra with Remicade in patients with ulcerative colitis or Crohn's disease (yet to begin recruitment).
 - NCT02096861 – a randomised phase III study comparing Inflectra with Remicade in patients with Crohn's disease (expected completion date of March 2017).

- NCT02148640 – a randomised, double blind study to evaluate the switching from Remicade to Inflectra in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease and psoriasis (NOR-SWITCH study). The estimated completion date for this study is May 2016.

Table 1: Trials and associated reports presented in the minor submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Study CT-P13 1.2 (no publications) (Study 1.2) Rheumatoid arthritis	EMA EPAR A randomized, double-blind, parallel-group, Phase 1 study to evaluate the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis: interim data as reported in EMA EPAR (27 June 2013) Clinical Study Report (CT-P13 1.2) A Randomized, Double-Blind, Parallel-Group, Phase I Study to Evaluate the Initial Pharmacokinetics, Efficacy, and Safety of CT-P13 Compared With Remicade When Co-administered With Methotrexate in Patients With Active Rheumatoid Arthritis	EMA EPAR 27 June 2013 - provided with minor submission. CSR 13 December 2013
Study CT-P13 1.1 Yoo et al 2013 ⁴ (Study 1.1) Ankylosing spondylitis	Clinical Study Report (CT-P13 1.1) A Randomized, Double-Blind, Parallel-Group, Phase 1 Study to Demonstrate the Equivalence with Respect to the Pharmacokinetic Profile of CT-P13 and Remicade in Patients with Ankylosing Spondylitis. Primary publication Yoo D, Miranda P, Piotrowski M et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study.	CSR 29 August 2013 (amended final report date) 2013 Annals of Rheumatic Diseases Oct;72(10):1613-20.
Study CT-P13 3.1 Park et al 2013 ⁵ (Study 3.1) Rheumatoid arthritis	Clinical Study Report (CT-P13 3.1) A Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Equivalence in Efficacy and Safety of CT-P13 Compared with Remicade when Co-administered with Methotrexate in Patients with Active Rheumatoid Arthritis Primary publication Park W, Hrycaj P, Kovalenko V. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study.	CSR 29 August 2013 (amended final report date) 2013 Annals of Rheumatic Diseases Oct;72(10):1605-12.

6.8 The key features of Study 1.2, Study 1.1 and Study 3.1 are presented in Table 2. Of particular note:

Study 1.2 and Study 3.1 were conducted in adult patients with active rheumatoid arthritis who were not receiving adequate response over at least 3 months from methotrexate alone.

With regard to the applicability of the presented evidence in patients with rheumatoid arthritis to the current PBS listing of infliximab:

- Prior treatment with biologics for RA was an exclusion criterion. The current PBS listing for Remicade permits prior use of biological disease modifying anti-rheumatic drugs (bDMARDs).
- Prior treatment with DMARDs in the preceding 6 months (except methotrexate or sulfasalazine) was an exclusion criterion. The current PBS listing for Remicade indicates that patients must have failed to achieve an adequate response to a trial of at least 6 months of at least 2 DMARDs for 3 months each, used either sequentially or in combination, with specific combinations and doses required to achieve eligibility.
- Methotrexate had to be dosed between 12.5mg to 25mg/week in the preceding 3 months for a patient to be eligible for the studies. The current PBS listing of Remicade requires that patients are receiving inadequate response to at least 20mg/week of methotrexate if tolerated, and in combination with other DMARDs, to be eligible.
- Patients were required to take methotrexate in combination with either Inflectra or Remicade. This is consistent with the current PBS listing of infliximab.
- The prior therapies in Study 1.2 and Study 1.3 in patients with rheumatoid arthritis differ from those required in the PBS listing for Remicade. The patients in these studies may have been responsive to standard DMARD therapy and would therefore not have required a biologic in the Australian setting.

Study 1.1 was conducted in adult patients with ankylosing spondylitis with a BASDAI score ≥ 4 despite conventional treatment for at least 3 months.

With regard to the applicability of the presented evidence in patients with ankylosing spondylitis to the current PBS listing of infliximab:

- Prior treatment with biologics for ankylosing spondylitis was an exclusion criterion. The current PBS listing for Remicade permits the prior use of bDMARDs.

6.9 As stated above, Study 1.2 and Study 3.1 both have extension studies (Study 1.3-NCT01571219 and Study 3.2-NCT01571206). Results from these studies were presented as additional evidence to support the substitution of Remicade with Inflectra. The extension studies switched patients after 54 weeks of Remicade to Inflectra and continued treatment up to week 102.

Table 2: Trial characteristics of the studies included in the minor submission

	Study 1.2	Study 1.1	Study 3.1
Patient population	Active rheumatoid arthritis not receiving adequate response to methotrexate	Active ankylosing spondylitis	Active rheumatoid arthritis not receiving adequate response to methotrexate
Number of participants	19	250	606
Study design	Randomised, phase I	Randomised, phase I	Randomised, phase III
Objective	Pilot study	PK equivalence	Therapeutic equivalence
Intervention	Inflectra 3mg/kg at week 0, 2, 6 then 8 weekly until week 102	Inflectra 5mg/kg at week 0, 2, 6 then 8 weekly until week 54.	Inflectra 3mg/kg at week 0, 2, 6 then 8 weekly until week 54.

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	Study 1.2	Study 1.1	Study 3.1
Comparator	Remicade 3mg/kg to week 54 then switch to Inflectra to week 102	Remicade dosing as for Inflectra	Remicade dosing as for Inflectra
Primary outcome	Peak serum concentration (C_{max}) at weeks 0, 2 and 6.	C_{max} and AUC after dose 5 (week 22 – 30)	ACR20 at week 30
Secondary outcomes	PK, PD, efficacy and safety	ASA20 and ASA40, BASDAI, BASFAI, BASMI, chest expansion and SF-36 at weeks 14, 30 and 54.	ACR50, ACR70, time to ACR20, DAS28, EULAR response criteria, CDAI, SDAI, SF-36 at weeks 14, 30 and 54
Additional PK outcomes		C_{av} , C_{min} , half-life, C_L and V_d measured after dose 5.	C_{max} , C_{min} , C_{av} and T_{max}
Other outcomes		Immunogenicity and AEs	Immunogenicity, pharmacodynamic assessments and AEs
Concomitant study medicines	Methotrexate and folic acid	Nil	Methotrexate and folic acid
Prior treatment with biologic	Not permitted	Not permitted	Not permitted
Study blinding	Double blind (unblinded after week 54)	Double blind	Double blind (unblinded after efficacy evaluation at week 30)
Duration of treatment	102 weeks (patients receiving Remicade switched to Inflectra at week 54)	Up to 54 weeks (primary study)	Up to 54 weeks (primary study)
Duration of follow-up	110 weeks	Up to 62 weeks (8 weeks after last dose)	Up to 62 weeks (8 weeks after last dose)
Crossover	All Remicade patients were switched to Inflectra after week 54.	Patients enrolled into extension study (after week 54) were switched from Remicade to Inflectra	Patients enrolled into extension study (after week 54) were switched from Remicade to Inflectra
Data following crossover	Safety	Safety, efficacy, immunogenicity	Safety, efficacy, immunogenicity

AE = adverse events; ACR = American College of Rheumatology; ACR20 / 50 / 70 = 20% / 50% / 70% improvement according to the ACR criteria; ASAS = Assessment of Spondyloarthritis International Society; BASDAI / FAI / MI = Bath Ankylosing Spondylitis Disease Activity Index / Functional Index / Metrology Index; CDAI = Clinical disease activity index; DAS = Disease Activity Score; EULAR = The European League Against Rheumatism; PD = pharmacodynamics; PK = pharmacokinetics; AUC = area under the concentration-time curve; C_{av} = average steady-state plasma drug concentration; C_L = apparent total body clearance of the drug; C_{max} = peak plasma drug concentration; C_{min} = minimum plasma drug concentration; T_{max} = time to maximum plasma concentration; V_d = apparent volume of distribution; T

6.10 Enrolled patient population and disposition in the studies is presented in the table below.

Table 3: Discontinuations and baseline characteristics of the studies included in the minor submission

	Study 1.2		Study 1.1		Study 3.1	
	Inflectra (n=9)	Remicade (n=9) ^a	Inflectra (n=125)	Remicade (n=125)	Inflectra (n=302)	Remicade (n=304)
Disposition						
Discontinuation due to:						
AE n (%)	3 (33.3)	1 (11.1)	10 (8.0)	8 (6.4)	31 (10.3)	41 (13.5)
Any reason (%)	5 (55.6)	4 (44.4)	19 (15.2)	21 (16.8)	69 (22.8)	82 (27.0)
Characteristics						
Age (years)						
Mean (SD)	51.6 (13.3)	47.1 (14.8)	39.2 (12.1)	38.7 (10.5)	49.0 (12.18)	48.6 (11.49)
Race n (%)						
White	0	0	97 (77.6)	92 (73.6)	220 (72.8)	222 (73.0)
Asian	9 (100%)	9 (100)	16 (12.8)	13 (10.4)	34 (11.3)	37 (12.2)
C-reactive Protein (mg/L)						
Mean (SD)	33.2 (38.2)	56.8 (41.5)	189.7 (237.4)	242.5 (307.1)	19.0 (25.1)	18.9 (21.9)
Erythrocyte Sedimentation Rate (mm/hour)						
Mean (SD)	65.0 (22.2)	83.4 (34.3)	35.5 (19.6)	37.1 (23.8)	46.5 (22.3)	48.5 (22.6)
Swollen Joint Count						
Mean (SD)	10.8 (4.8)	15.1 (5.4)	na	na	16.2 (8.7)	15.2 (8.3)
Tender Joint Count						
Mean (SD)	11.6 (3.4)	19.3 (9.3)	na	na	25.4 (13.4)	23.9 (13.0)
Baseline BASDAI score n (%)						
≥8	na	na	33 (26.4)	30 (24.0)	na	na

^a10 patients were randomised to Remicade in Study 1.2; however one patient was dosed with Inflectra at Dose 2 and has been excluded from the statistical analyses.

AE = adverse events; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; SD = standard deviation.

- 6.11 Baseline characteristics are similar across arms in the two large randomised studies (Study 1.1 and Study 3.1).
- 6.12 The mean number of tender joints are greater in the Remicade arm of Study 1.2, but the small number of patients (n=18) makes this difficult to interpret.
- 6.13 In Study 3.1 in rheumatoid arthritis, methotrexate and folic acid were taken by all patients concurrently with either Inflectra or Remicade. The dose of methotrexate in each arm was similar for the duration of the study.
- 6.14 The Supplementary Clinical Section to the submission included a list of uncontrolled studies involving the use of Inflectra in patients with Crohn's disease and ulcerative colitis. These studies are presented in Table 4:

Table 4: Trials and associated reports presented in the supplementary clinical section to the minor submission

Trial ID	Protocol title/ Publication title	Publication citation
Study CT-P13 PMS Study Korea (no publications)	Interim Clinical Study Report Post-Marketing Surveillance of REMSIMA™ 100 mg (Infliximab) (monoclonal antibody, recombinant) to Evaluate Its Safety and Efficacy in Korea. Interim report, 30 Jan 2015	Interim CSR 30 January 2015 (provided as appendix 3 to the supplementary clinical section)
Norway Hospital Study (no publications)	Interim Report: Post-marketing real-world clinical experience with REMSIMA™ 100 mg (infliximab) (monoclonal antibody, recombinant) in patients with inflammatory bowel disease at Akershus University Hospital, Norway.	Interim Report 2 April 2015 (provided as appendix 4 to the supplementary clinical section)
Czech Rep. Clinical Study (no publications)	Interim Report: Post-marketing real-world clinical experience with REMSIMA™ 100 mg (infliximab) (monoclonal antibody, recombinant) in patients with inflammatory bowel disease at IBD Clinical and Research Centre, ISCARE Lighthouse and Charles University, Prague, Czech Republic.	Interim Report 24 April 2015. (provided as appendix 5 to the supplementary clinical section)
Hungary Multicentre Study (no publications)	Clinical Study Report: The investigation of disease outcome in patients with inflammatory bowel diseases on biological therapy with measurement of anti-TNF and anti-TNF-antibodies serum levels: a multi-center, prospective clinical study.	CSR 1 April 2015 (provided as appendix 6 to the supplementary clinical section)
Paediatric poster data (3 posters presented at ECCO, Spain)	Reports: Jarzebicka D, et al, Preliminary assessment of efficacy and safety of switching between originator and biosimilar infliximab in paediatric Crohn disease patients. (Poster No. 295) Sieczkowska, J et al, Assessment of safety and efficacy of biosimilar infliximab in children with Crohn disease: a preliminary report. (Poster No.430) Jarzebicka, D et al, First observations of the use of biosimilar infliximab for treatment of ulcerative colitis in paediatric population. (Poster No.456)	Presented at the 10th Congress of ECCO Spain.

CSR = clinical study report; ECCO = European Crohn's and Colitis Organisation; IBD = inflammatory bowel disease; TNF = tumour necrosis factor.

- 6.15 Interim reports or clinical study reports have been provided for the four post-market studies referenced by the supplementary clinical section. The sponsor has stated: "The demographics and baseline characteristics reported show that patients had active moderate-severe IBD, consistent with the intended PBS population for Inflectra".
- 6.16 The number of patients and exposure to Inflectra in the post-market studies are given in Table 5.

Table 5: Number of patients enrolled in the Inflectra post-market studies (PMS) for inflammatory bowel disease indications and the median number of doses received

	Korea	Hungary	Norway	Czech Rep.
Number of patients				
Crohn's Disease	83	90	41	78
Ulcerative Colitis	78	51	30	33
Fistulising Crohn's Disease	12	0	3	29
Total	173	141	74	140
Proportion with prior Remicade use	35%	NR	8%	11% ^a
Proportion with prior bDMARD use (incl. Remicade)	35%	26%	24%	74%
Median number of doses of Inflectra				
Crohn's Disease	5	3	3	3
Ulcerative Colitis	5	3		
Fistulising Crohn's Disease	5	3		

^aAt least 11% of patients in this study had prior exposure to Remicade. Eight patients with fistulising Crohn's Disease did have prior exposure to anti-TNF agents but the agent was not recorded.

- 6.17 The efficacy endpoints for these post-market studies include the proportion of patients achieving a response and/or remission.

Comparative effectiveness in patients with rheumatoid arthritis

- 6.18 Study 1.2 is based on 19 enrolled patients with rheumatoid arthritis. One patient was excluded from the analysis due to a major protocol violation. No formal sample size calculation was performed as this study was primarily designed to inform the larger Phase III Study 3.1. With the exception of implications of switching from Remicade to Inflectra after week 54, the results of this study are not discussed further.
- 6.19 Study 3.1 was powered (80%) to detect a 2-sided equivalence margin of 15 percentage points in the proportion of patients achieving ACR20, assuming a responder rate of 50% and the exclusion of 20% of patients from the per-protocol population.
- 6.20 The trial results for the ACR20 (primary outcome), ACR50, ACR70 and DAS28 for Study 3.1 are summarised in the table below.

Table 6: Clinical efficacy outcomes for Study 3.1 in rheumatoid arthritis

	Week ^b	Population	Inflectra n/N (%)	Remicade n/N (%)	Estimate of Treatment Difference ^a	95% CI of the treatment difference
American College of Rheumatology definition of a 20% improvement						
ACR20	30	ITT	184/302 (60.9)	178/304 (58.6)	0.02	-0.06, 0.10
		PP	180/246 (73.2)	174/250 (69.6)	0.04	-0.04, 0.12
ACR20	14	PP	179/246 (72.8)	161/250 (64.4)	0.08	0.00, 0.17
ACR20	54	PP	168/246 (68.3)	155/250 (62.0)	0.06	-0.02, 0.15
ACR50	30	PP	106/246 (43.1)	100/250 (40.0)	0.03	-0.06, 0.12
ACR70	30	PP	50/246 (20.3)	45/250 (18.0)	0.02	-0.05, 0.09
Disease Activity Score ^{cd}						
			N Mean (SE)	N Mean (SE)	Estimate of Treatment Difference	95% CI of the treatment difference
DAS28 (ESR)	30	PP	243 4.2 (0.08)	248 4.31 (0.08)	-0.11	-0.34, 0.12
DAS28 (CRP)	30	PP	244 3.6 (0.08)	248 3.66 (0.08)	-0.06	-0.30, 0.17

ACR20 = American College of Rheumatology definition of a 20% improvement; CI = confidence interval; CRP = c-reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; ITT = all randomised population; PP = per protocol population; SE = standard error.

^aEstimate of the difference in proportions between Inflectra and Remicade using the exact binomial test.

^bPatients have received 6 doses of study drug by Week 30.

^cThe calculation of DAS28 (ESR), and DAS (CRP) is presented on p72, Study 3.1 CSR. DAS28 is a combined index that incorporates the number of tender and swollen joints, ESR and a measure of general health using a visual analogue scale. An alternative DAS28 formula incorporates CRP rather than ESR. See the DAS-score website (accessed 19/05/2015).

^dDAS28 adjusted least squares mean, SE and difference of means are calculated using an ANCOVA model with baseline DAS28, geographic region and CRP category as covariates.

- 6.21 Approximately 60% of randomised patients achieved ACR20 in both the Inflectra and Remicade arms in Study 3.1. The 95% confidence interval for the difference in treatment effect at week 30 between the groups was contained within the pre-specified 15% equivalence margin. A sensitivity analysis using logistic regression controlling for geographical region and categorised baseline CRP reported similar results (95% CI for the ITT population: -0.05, 0.10).
- 6.22 Patients receiving Inflectra and Remicade had a similar mean DAS28 at week 30 after controlling for baseline DAS28, geographic region and baseline CRP. A clinically important improvement for DAS28 (ESR) is approximately -1.2 and for DAS28 (CRP) is -1.0. The 95% CI limits of difference between Inflectra and Remicade are smaller than a clinically important change. DAS28 is a combined index derived from the count of tender and swollen joints, a measure of general health and either ESR or CRP, with lower scores indicating lower disease activity. The index has been widely used and validated in patients with rheumatoid arthritis and in patients receiving infliximab.
- 6.23 Inflectra and Remicade were similar in terms of other clinical efficacy outcomes presented in the CSR for Study 3.1: patient pain, global assessment of disease activity, physical ability, change from baseline in ESR and CRP and quality of life (measured using SF-36).

Comparative effectiveness in patients with ankylosing spondylitis

- 6.24 Study 1.1 was a pharmacokinetic study powered (90%) to detect a 2 sided equivalence margin of 80% to 125% for AUC_{τ} and $C_{max,ss}$, allowing for a dropout rate of 20%. As well as pharmacokinetic outcomes, Study 1.1 reported on the proportion of patients achieving a 20% improvement on the Assessment of SpondyloArthritis International Society (ASAS) scale (ASAS20), a 40% improvement on the same scale (ASAS40), mean change from baseline in BASDAI^b, BASFI and BASMI and mean change from baseline in chest expansion. Table 7 provides the equivalency results at weeks 14, 30 and 54 as measured using ASAS20 and ASAS40.

Table 7: ASAS20 and ASAS40 at weeks 14, 30 and 54 in patients taking Inflectra compared with Remicade

	Week ^b	Population	Inflectra n/N (%)	Remicade n/N (%)	Estimate of Treatment Difference ^a	95% CI of the treatment difference
Assessment of SpondyloArthritis International Society 20% and 40% improvement scale						
ASAS20	14	ITT	72/115 (62.6)	79/122 (64.8)	-0.02	-0.14, 0.10
	30	ITT	79/112 (70.5)	84/116 (72.4)	-0.02	-0.14, 0.10
	54	ITT	71/106 (67.0)	75/108 (69.4)	-0.02	-0.15, 0.10
ASAS40	14	ITT	48/115 (41.7)	56/122 (45.9)	-0.04	-0.17, 0.08
	30	ITT	58/112 (51.8)	55/116 (47.4)	0.04	-0.09, 0.17
	54	ITT	58/106 (54.7)	53/108 (49.1)	0.06	-0.08, 0.19

^aTreatment difference (absolute difference in percentage of patients achieving ASAS20 or ASAS40) was calculated during the evaluation using the cohort study risk-ratio calculator in Stata® 13.1.

- 6.25 No difference in the rates of patients achieving ASAS20 or ASAS40 were observed in Study 1.1. However, the calculated confidence intervals for the absolute difference between the groups includes differences of up to 19%. As stated above, Study 1.1 was powered to detect differences in pharmacokinetic rather than effectiveness outcomes.
- 6.26 The CSR reported the odds ratio for achieving ASAS20 or ASAS40 with Inflectra compared with Remicade derived from a logistic model controlling for geographical region and baseline BASDAI. The confidence intervals for the odds ratio included 1 (no statistically significant difference).

Pharmacokinetic analyses**Pharmacokinetic analyses of Study 1.1 (AS) and Study 3.1 (RA)**

- 6.27 Study 3.1: Mean serum concentration of Inflectra over time was similar to Infliximab in both the pharmacokinetic population and the antibody negative subgroup. No differences in pharmacokinetics between Inflectra and Infliximab in Study 3.1 were highlighted during the TGA evaluation.
- 6.28 Study 1.1: Mean serum concentration of Inflectra over time was similar to Infliximab in both the pharmacokinetic population and the antibody negative subgroup. AUC_{τ} and $C_{max,ss}$ were similar for Inflectra and Infliximab in both the pharmacokinetic population and the antibody negative subgroup. The Delegate's overview indicated

^b Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Functional Index (BASFI) and Metrology Index (BASMI).

that the AUC results for the antibody positive subgroup were outside the normal bioequivalence limits of 80-125% but were within the bioequivalence limits for C_{max} . The antibody positive population was small (32 patients in the Inflectra arm and 34 patients in the Infliximab arm) so there was unlikely to be sufficient power to determine bioequivalence between the groups. This subgroup was defined by an outcome of treatment, so randomisation could not be stratified and imbalances in other (possibly confounding) characteristics between the groups cannot be ruled out. The sponsor has confirmed that Study 1.1 was not powered to detect a difference in AUC_{τ} in the antibody positive population.

- 6.29 The ACPM advised that “The PK data on comparison of the biosimilar to the innovator support the premise that PK characteristics were comparable in the studies and that there was no difference in the rate of formation of anti-drug antibodies”.
- 6.30 The ACPM noted that the PK dataset “had only been obtained over a limited dose range (3-5mg/kg every 8 weeks)” and stated that this dose may be increased to 10mg/kg every 6-8 weeks in IBD conditions. The maximum PBS subsidised dose for Remicade is 5mg/kg for all indications with the exception of rheumatoid arthritis, for which it is 3mg/kg. Therefore, the pharmacokinetic dataset provided to the TGA is relevant to the dose ranges currently reimbursed through the PBS. The ACPM noted that “the clinical evaluator was satisfied that PK comparability between test and reference had been demonstrated”.
- 6.31 The sponsor provided additional evidence regarding pharmacokinetic equivalence between Inflectra and Infliximab at doses greater than 5mg/kg (provided as Appendix 8 to the supplementary clinical section). The report concluded:

“no pharmacokinetic differences were observed between Remicade and CT-P13 [Inflectra] and pharmacokinetics of CT-P13 was expected to be linear in the dose range of 3-10mg/kg.”

Comparative effectiveness in patients with psoriatic arthritis

- 6.32 The minor submission did not provide evidence addressing the comparative effectiveness of Inflectra and Remicade in patients with severe active psoriatic arthritis.
- 6.33 The ACPM noted that while there were some differences between rheumatoid arthritis and psoriatic arthritis, some therapeutic targets are the same and extrapolation to this indication was acceptable.

Comparative effectiveness in patients with psoriasis

- 6.34 The minor submission did not provide evidence addressing the comparative effectiveness of Inflectra and Remicade in patients with severe chronic plaque psoriasis.
- 6.35 The ACPM agreed that, “since binding sTNF α appears to be a major mode of action of TNF antagonists in psoriasis, extrapolation to psoriasis is acceptable”.

Comparative effectiveness in patients with Crohn’s disease and ulcerative colitis

- 6.36 The minor submission did not provide evidence addressing the comparative effectiveness of Inflectra and Remicade in patients with Crohn’s disease, fistulising Crohn’s disease, Crohn’s disease in paediatric patients or moderate to severe or acute severe ulcerative colitis.
- 6.37 The ACPM initially considered, based on the provided evidence, that it was difficult to “justify extrapolation to IBD from the single RA pivotal trial data.”. The ACPM was concerned about a difference in the binding affinity of Inflectra compared with Remicade at the FcγRIIIa binding site, which may be important in IBD conditions.
- 6.38 In the response to the ACPM’s concerns, the sponsor provided a discussion of the relevance of FcγRIIIa binding, and whether differences in the affinity of binding would be detected using assays more representative of an *in vivo* disease model. In addition, the sponsor provided a supplementary clinical section to the minor submission that included data from 4 post-marketing studies in patients with Crohn’s disease, fistulising Crohn’s disease and ulcerative colitis. In total, the reports present data on 528 patients.
- 6.39 The results presented in the post marketing studies are not controlled, and thus do not inform comparisons between Inflectra and Remicade. Although a proportion of the patients in these studies had received infliximab or other bDMARDs previously there are no data available that provide an indication of patient response to the reference product relative to the response while receiving the biosimilar. Patients with Crohn’s disease or ulcerative colitis did respond to treatment with Inflectra, irrespective of prior exposure to bDMARDs.
- 6.40 The ACPM subsequently recommended that Inflectra has a positive benefit-risk profile for the proposed IBD indications (Crohn’s disease, fistulising Crohn’s disease and ulcerative colitis).

Comparative Harms

- 6.41 Study 3.1 and Study 1.1 reported a similar number of doses received, and a similar total dose administered for the Inflectra and Remicade arms. The rates of adverse events were similar across arms.

Table 8: Adverse events in Study 3.1 and Study 1.1

	Study 3.1 Rheumatoid arthritis		Study 1.1 Ankylosing spondylitis	
	Inflectra N=302	Remicade N=300	Inflectra N=128	Remicade N=122
Mean number of doses (SD)	8.0 (2.07)	7.9 (2.08)	8.4 (1.69)	8.5 (1.51)
Mean total dose administered mg (SD)	1712.4 (608.3)	1672.8 (595.1)	3186.7 (969.1)	3258.0 (861.5)
Treatment emergent AEs	732	738	362	375
Patients (%) with TEAE	213 (70.5)	211 (70.3)	95 (74.2)	82 (67.2)
Treatment emergent SAE	49	39	12	11
Patients (%) with TE SAE ^a	42 (13.9)	31 (10.3)	10 (7.8)	8 (6.6)
Patients (%) with TEAE leading to discontinuation ^b	33 (10.9)	47 (15.7)	11 (8.6)	9 (7.4)
Patients (%) with TEAE due to infection	127 (42.1)	137 (45.7)	55 (43.0)	49 (40.2)
Patients (%) with TEAE due to infusion-related reactions	10 (3.3)	11 (3.7)	0	4 (3.3)

AE = adverse event; SAE = serious adverse event; SD = standard deviation; TE = treatment emergent.

^aRisk difference between Inflectra and Remicade in Study 3.1 = 3.6% (-1.6%, 8.8%).

^bRisk difference between Inflectra and Remicade in Study 3.1 = -4.7% (-10.2%, 0.7%)

- 6.42 Both the Clinical Evaluation Report and the Delegate's report identified a differential rate of tuberculosis in patients receiving Inflectra compared with those receiving Remicade. In the CT-P13 clinical trial program, 1.6% (7/440) patients receiving Inflectra compared with 0.2% (1/431) patients receiving Remicade reported active tuberculosis. The sponsor stated that 3 cases were unconfirmed in patients receiving Inflectra, and two of these cases had abnormal chest x-rays, indicative of a history of TB at enrolment, which represents a protocol violation.
- 6.43 The sponsor states that the incidence of TB in the CT-P13 trial program was broadly in line with previous Remicade studies (0.9% for confirmed cases and 1.6% for all cases).
- 6.44 The ACPM noted the sponsors input and agreed that differences may be related to the higher prevalence of TB or variability in screening of TB in the countries where the trial programme was conducted. However, the ACPM stated that there is "insufficient evidence to discount the possibility that there are different rates of TB activation for this biosimilar product compared to the incidence with Remicade." Despite the potential difference, the ACPM advised that Inflectra had a similar safety profile to Remicade.
- 6.45 In the post-market study data provided with the supplementary clinical section (n=528 across 4 studies), only one case of TB was identified (in the Korean PMS).

Pharmacovigilance

- 6.46 The TGA has accepted the EU Risk Management Plan Version 4.0 and the Australian Specific Annex Version 1.0. In addition to a risk management plan, the sponsor will be required to submit the results of patient registries and ongoing clinical trials to the TGA.

Clinical claim

- 6.47 The submission has provided evidence from three randomised controlled trials and two extension studies. At enrolment into the extension studies, patients were switched from Remicade to Inflectra.
- 6.48 The evidence supports the conclusion that Inflectra and Remicade were:
- similar in terms of efficacy in rheumatoid arthritis (proportion of patients achieving ACR20)
 - similar in terms of efficacy in ankylosing spondylitis (proportion of patients achieving ASAS20),
 - similar in terms of safety as advised in the ACPM outcomes report
- 6.49 A claim of equivalent effectiveness and equivalent safety of Inflectra compared with Remicade is consistent with the submission's premise of biosimilarity.
- 6.50 The PBAC noted that the ACPM was satisfied that the submitted data showed that Inflectra is similar to Remicade in terms of efficacy and safety, further noting that the ACPM stated there were sufficient data to declare Inflectra a biosimilar for Remicade. Therefore, this claim is appropriate.

Substitution between the biosimilar and the reference biologic

- 6.51 Both Study 3.1 and Study 1.1 had extension studies (after 54 weeks of treatment and up to 102 weeks of treatment). In both studies, patients originally randomised to Remicade were switched to Inflectra. For the treatment of RA, 128 patients received Inflectra following Remicade, and for the treatment of AS, 76 patients received Inflectra following Remicade. Patients and treating physicians remained blinded to the treatment received during the randomised phase of Study 3.1 during the extension study. Whether or not blinding of original treatment allocation is maintained for the extension of Study 1.1 is not reported. The findings of the extension are:
- No significant loss of efficacy determined by ASAS20 / ASAS40 for ankylosing spondylitis and ACR20, ACR50 and ACR70 for rheumatoid arthritis.
 - No notable differences in AEs, SAEs and AEs of special interest.
 - No differences in immunogenicity testing
 - No special risk in switching from Remicade to Inflectra.
- 6.52 The Clinical Evaluation Report concluded:
- “Overall, the results of the 2 extension studies in terms of efficacy, safety and immunogenicity analyses were consistent in all datasets supporting the robustness of the findings in the CT-P13 clinical development program with respect to biosimilarity with Remicade®.”
- 6.53 The number of patients enrolled in the extension studies was lower than in the initial studies.

Table 9: Number of patients enrolled in the included studies and enrolled in the extension studies.

Patients remaining on treatment	Initial Inflectra patients	Initial Remicade patients
Study 1.1		
Week 0 (Dose 1)	128	122
Week 54 (Dose 9)	109	104
Extension Study 1.3		
Week 62 (Dose 10)	90	84
Week 102 (Dose 15)	84	76
Study 3.1		
Week 0 (Dose 1)	302	300
Week 54 (Dose 9)	237	220
Extension Study 3.2		
Week 62 (Dose 10)	158	143
Week 102 (Dose 15)	141	128

- 6.54 The baseline characteristics of those patients entering the extension studies were not discussed in the submission. Patients at greatest risk of adverse events may not have been enrolled in the extension studies as they are more likely to have discontinued prior to the extension study than those patients who have few, or are able to tolerate, adverse events associated with infliximab. It is unclear whether this would minimise observed differences in safety or efficacy post-switch (if there are any differences).
- 6.55 Study 1.2 (N=19) had an extension phase (following week 54) in which patients receiving Remicade were switched to Inflectra. The number of AEs after week 54 in the arm that switched from Remicade was similar to the arm that continued on Inflectra. No hypersensitivity events occurred following switching. The Clinical Evaluation Report concluded that the extension phase of Study 1.2, “did not reveal any new safety concerns, particularly with respect to immunogenicity potential”.
- 6.56 Celltrion Healthcare, the international sponsor for Inflectra, has claimed:
- “Based on the totality of the clinical data from main and extension AS and RA studies it can be concluded that CT-P13 not only demonstrates highly similar efficacy, safety and immunogenicity features in AS and RA patients who were infliximab-naïve but also displays consistently similar efficacy, safety and immunogenicity attributes following a single transition of Remicade® treated AS and RA patients on CT-P13.”
- 6.57 The absence of identified changes in efficacy, safety and immunogenicity following switching from the reference biologic (Remicade) to Inflectra supports the non-inferiority of Inflectra to Remicade, particularly for the indications enrolled in the two studies (rheumatoid arthritis and ankylosing spondylitis).
- 6.58 Although no special safety concerns have been identified in the presented data regarding switching, adequate monitoring of patients by suitably qualified specialists may minimise risks associated with the use of infliximab, whether the innovator or biosimilar drug. The current PBS restrictions for infliximab require that treatment is prescribed by a consultant specialist with expertise in the indication in which

infliximab is being used^c. This is also stated in the current product information for Remicade and the proposed product information for Inflectra. In addition, specialists are required to regularly monitor patients (usually between infliximab doses) to assess the level of response, which is required for the ongoing provision of subsidised drug. The requirement that patients have ongoing management by specialist consultants may minimise the risk of adverse events as well as any issues associated with substitution of Remicade for Inflectra, or vice versa.

- 6.59 Infusion related reactions are a potential safety issue for both Remicade and Inflectra. Although there were no identified differences in infusion-related reactions between the Inflectra and Remicade arms of the pivotal studies, and no special risk of infusion-related reactions identified following switching from Remicade to Inflectra, as the administration of Remicade and Inflectra is supervised, any concerns regarding infusion-related reactions, particularly following switching, are likely to be minimised. The proposed PI recommends infusions over a period of not less than 2 hours with patients observed for at least one to two hours post infusion for side effects.
- 6.60 A switching study is currently underway that is enrolling patients across all infliximab indications (NOR-SWITCH study), and is expected to be completed in May 2016.

Economic analysis

- 6.61 Equi-effective dose: 100mg Inflectra = 100mg Remicade. This is claimed to be based on the clinical efficacy studies and pharmacokinetic studies.
- 6.62 Cost-minimisation analysis: Given the claim of dose equivalence, the sponsor compares unit prices only. The current listing (price of Remicade, ex-manufacturer: \$[REDACTED]/100mg vial) is compared to the proposed listing where the statutory 16% price reduction to the current ex-manufacturer price is applied (the ex-manufacturer price of both Inflectra and Remicade: \$[REDACTED]/100mg vial). Cost savings are therefore anticipated with the proposed listing.

Estimated PBS usage & financial implications

Estimated Usage

- 6.63 The minor submission presented estimates of infliximab (Remicade/Inflectra) usage for the Years 2016-2020.
- 6.64 Historical PBS data on infliximab usage from 2010-2014 is used to identify market trends. Extrapolation from the total usage identified in 2014 assumes ongoing and increasing growth across the total infliximab market.

^c Acceptable prescribers for infliximab in the PBS listing of Remicade are: a gastroenterologist or internal / general medicine consultant specialising in gastroenterology for IBD conditions, with consultation with a paediatric gastroenterologist for children; a dermatologist for psoriasis; a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis for the rheumatoid arthritis indication; and, a rheumatologist for the ankylosing spondylitis indication.

- 6.65 The PBS usage data, disaggregated by private/public sector and by indication is provided in the Financial Estimates Workbook. It is noted that the data used in the financial estimates does not include data on item 4284L (RPBS only listing), nor items 10184B, 10196P (where usage data begins in 2015). This increases the likelihood that the projections are underestimates.
- 6.66 Summary data, with calculated growth rates, are shown in the table below;

Table 10: PBS use of infliximab and market growth 2010-2014

PBS data	2010	2011	2012	2013	2014	2010-2014
	# services	# services (growth on previous)*	# services (growth on previous)*	# services (growth on previous)*	# services (growth on previous)*	Average growth
Total for indications of RA, AS, PSA and PSO	8,382	8,413 (+0.4%)	8,950 (+6.4%)	9,636 (+7.7%)	10,747 (+11.5%)	+6.5%
Total for indications of CD and UC	5,339	7,494 (+40.4%)	9,680 (+29.2%)	13,972 (+44.3%)	18,506 (+32.5%)	+35.3%
TOTAL - ALL INDICATIONS	13,721	15,907 (+15.9%)	18,630 (+17.1%)	23,608 (+26.7%)	29,253 (+23.9%)	+22.6%

RA = rheumatoid arthritis, AS = ankylosing spondylitis; PSA = psoriatic arthritis; PSO = plaque psoriasis; CD = Crohn's disease (in this table this includes paediatric use and fistulising disease); UC = ulcerative colitis.

- 6.67 As acknowledged by the submission, market growth rates are not consistent across indications. Ongoing high growth in usage has been driven by the bowel-related indications (growing on average by 35% p.a.), while there is substantially lower growth in the use for rheumatoid arthritis, AS and psoriatic indications (around 7% p.a., although also with an increasing trend).

Projected usage across all indications

- 6.68 When estimating projected future use of infliximab, the submission used an initial market growth rate of 21.8% (for 2015) based on the average overall PBS market growth over the years 2011-2014. In keeping with the trend of increasing growth, the rate is increased, somewhat arbitrarily, for the projections of service usage 2016-2020 (shown below).

Table 11: Projected growth rate and number of services of infliximab across all indications 2015-2020 (submission's estimates).

Year	2014	2015	2016	2017	2018	2019	2020
	(Baseline data)	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Growth rate	(Baseline data)	21.8%*	█%	█%	█%	█%	█%
No. of services	29,253	35,630	█	█	█	█	█

Financial implications to the PBS

- 6.69 The submission did not anticipate the listing of Inflectra will impact the size or growth of the overall infliximab market, therefore all quantitative financial implications relate to the statutory 16% price reduction associated with listing of a biosimilar.

- 6.70 The submission did not account for any impact of price disclosure.
- 6.71 The redacted table below shows that the minor submission estimated a net saving to the PBS of \$30 - \$60 million in Year 5 of listing, with a total net saving to the PBS of more than \$100 million over the first 5 years of listing.

Table 12: Net projected savings to the PBS/RPBS due to listing of Inflectra for all infliximab indications

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Without Inflectra listing: Net cost to PBS/RPBS of Remicade	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
With Inflectra listing: Net cost to PBS/RPBS of Inflectra and Remicade	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total savings to PBS/RPBS with listing Inflectra	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total savings over 5 years	\$ [REDACTED]				

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of infliximab (Inflectra) as a biosimilar of infliximab (Remicade), on a cost-minimisation basis to infliximab (Remicade), where the equi-effective doses are 100 mg infliximab (Inflectra) and 100 mg infliximab (Remicade). The PBAC recommended that the same indications that apply to infliximab (Remicade) should apply to infliximab (Inflectra). All listings for Remicade are currently under the Section 100 Highly Specialised Drugs Program and the current PBS indications are:
- Acute severe ulcerative colitis
 - Moderate to severe ulcerative colitis
 - Severe refractory Crohn’s disease
 - Refractory fistulising 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 Inflectra is similar to Remicade in terms of efficacy and safety, further noting that the ACPM stated there were sufficient data to declare Inflectra a biosimilar for Remicade.
- 7.3 The PBAC advised the Minister that it considered the Remicade and Inflectra 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. 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.

- 7.4 In forming its view on brand substitution (“a” flagging), the PBAC considered a range of factors including:
- There is evidence from three randomised clinical trials in treatment-naïve patients initiating on either Inflectra or Remicade that support a finding that Inflectra has equivalent effectiveness and equivalent safety compared to Remicade.
 - The key randomised clinical studies in rheumatoid arthritis and ankylosing spondylitis did not indicate differences in efficacy or safety of Inflectra compared with Remicade. The supportive evidence from a series of non-comparative studies in patients with Crohn’s disease or ulcerative colitis demonstrates treatment with Inflectra is also effective and safe in these conditions.
 - The clinical data provided in the submission did not suggest that there were any identified populations where the risks of using the biosimilar product in place of the reference biologic are disproportionately high.
 - In the two trials with extension studies (Study 1.1 and Study 3.1), switching from Remicade to Inflectra occurred, and the clinical evidence suggested no difference in efficacy, safety or immunogenicity between the biosimilar and reference biologic in these studies.
 - The ACPM has declared Inflectra a biosimilar for Remicade. The ACPM was satisfied of the similar safety and efficacy of Inflectra and Remicade in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis and Crohn’s disease.
- 7.5 The PBAC noted the consumer comments on Inflectra that expressed concern at the perceived risks that may arise as a result of substitution and switching with Remicade. The PBAC further noted the comments made by various patient and clinician groups at the PBAC hearing on biosimilar medicines particularly in relation to pharmacy level substitution. The PBAC was conscious that many, although not all, consumer and clinical representatives at the forum were concerned that automatic pharmacy level substitution would entail risks for patients. The PBAC noted that some of these concerns appear to be based on the misunderstanding that pharmacy-level substitution is automatic or that pharmacists routinely ignore prescriber directions not to substitute.
- 7.6 The PBAC noted that another concern raised in the stakeholder consultation related to the ability to track the use of a biosimilar and the reference biologic in a patient in order to assess if any differences in safety or efficacy were related to product switches. The PBAC noted that Medicare routinely collects information on the brand of drug that is dispensed for a patient.
- 7.7 Consumers and clinicians were also concerned that pharmacy-level substitution of infliximab will lead to repeated switching from the biosimilar to the reference product and back. The PBAC considered this unlikely to occur in practice because infliximab

is administered via an infusion with most patients receiving all courses of treatment at a single centre, reducing the likelihood of switches between brands.

- 7.8 The PBAC recommended that the Department develop an implementation strategy for infliximab for PBAC's review before an "a" flag can be included against the Inflectra and Remicade brands on the Schedule. This implementation strategy should include an education campaign designed to support and promote the use of biosimilars, improving awareness and confidence by both health professionals and consumers to choose these products.
- 7.9 The PBAC reiterated its position that it would consider the marking of equivalent (i.e. "a" flagging) in 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.
- 7.10 The PBAC considered that while the market for infliximab is growing in the IBD indications, the listing of Inflectra is unlikely to cause any additional expansion in the market. The PBAC noted that the submission estimated net overall savings to the PBS of more than \$100 million over the first five years of listing. This was based on the impact of the statutory 16% price reduction following the listing of a biosimilar brand. The financial estimates did not account for any potential impacts of price disclosure.
- 7.11 The PBAC advised that Inflectra is not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

Listings same as for infliximab (Remicade).

9 Context for Decision

- 9.1 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 welcomes the PBAC's recommendation to list INFLECTRA (infliximab) on the PBS. We welcome the opportunity to continue the conversation with all healthcare stakeholders so that INFLECTRA can be responsibly introduced into the healthcare system for the benefit of doctors and patients. We recognise the doctor patient relationship is paramount. The sponsor did not seek 'a'-flagging within this submission.