

5.24 TOFACITINIB
5 mg tablet
Xeljanz®; Pfizer Australia Pty Ltd

1 Purpose of Application

1.1 The major submission sought an Authority Required listing for the treatment of severe active rheumatoid arthritis (RA) in patients meeting certain criteria.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TOFACITINIB				
<u>Initial Treatment</u> Tablet 5 mg, 56	1	3	\$ [REDACTED] (effective price: \$ [REDACTED])	Xeljanz® PF
<u>Continuing treatment</u> Tablet 5 mg, 56	1	5	\$ [REDACTED] (effective price: \$ [REDACTED])	

Abbreviated version

Treatment phase: Initial 1 (new patient or patient re-commencing after a break of more than 24 months)	
Condition	Severe active rheumatoid arthritis
Restriction	Authority required
Clinical criteria	The patient must have severe active rheumatoid arthritis. AND Patient must have received no PBS-subsidised treatment with a bDMARD or tofacitinib for this condition in the previous 24 months AND Patient must have failed, in the 24 months immediately prior to the date of application, to achieve an adequate response to at least 6 months of intensive treatment with disease modifying anti-rheumatic drugs (DMARDs), which must include at least 3 months continuous treatment with each of at least 2 DMARDs, one of which must be methotrexate at a dose of at least 20 mg weekly and one of which must be: (i) hydroxychloroquine at a dose of at least 200 mg daily; or (ii) leflunomide at a dose of at least 10 mg daily; or (iii) sulfasalazine at a dose of at least 2 g daily. AND Patient must not receive more than 16 weeks treatment under this restriction.

2.1 The requested restriction did not require the concomitant use of methotrexate. This was consistent with the proposed TGA registered indication which permits monotherapy or combination treatment with non-biological DMARDs.

2.2 The requested twice daily dosing regimen was consistent with dosing regimen used in the trials presented in the submission. However, the ESC noted that the trials also used a 10 mg dose of tofacitinib which is not TGA-approved and for which the sponsor is not seeking listing.

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

3 Background

- 3.1 Tofacitinib was included in the Australian Register of Therapeutic Goods on 5 February 2015. Tofacitinib is TGA registered for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Tofacitinib can be used alone or in combination with non-biological DMARDs, including methotrexate. Therapy with tofacitinib should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.
- 3.2 This was the first submission to the PBAC for tofacitinib. A submission had earlier been lodged for consideration at the July 2013 PBAC meeting but was withdrawn by the sponsor before consideration by the ESC or the PBAC. A Commentary on the July 2013 submission had been prepared for the July 2013 PBAC meeting.
- 3.3 In the fourth-round of assessment, the TGA Evaluator in the December 2013 Clinical Evaluation Report was unable to recommend approval as the proposed indication did not reflect the status of tofacitinib as a third line agent but was prepared to do so if the indication was revised to reflect use as a third line agent as opposed to a second line agent.
- 3.4 The TGA Delegate, in the most recent 'Request for ACPM Advice' from December 2013, was in agreement with the Evaluator with respect to limiting tofacitinib to third line therapy.
- 3.5 At the February 2014 ACPM meeting, the ACPM resolved to approve tofacitinib for use as third line therapy only after the use of DMARDs and at least two bDMARDs.
- 3.6 The sponsor appealed the decision to approve tofacitinib use limited to third line therapy in August 2014. The initial decision to not allow use in the second line setting was revoked and this revocation was outlined in a letter to the sponsor in October 2014. The Minister's delegate was satisfied that tofacitinib could be used as second line therapy after an inadequate response or intolerance to methotrexate as monotherapy or in combination with a DMARD, including methotrexate.

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

4 Clinical place for the proposed therapy

- 4.1 RA is an autoimmune disease that causes pain, inflammation and swelling in the lining of joints and surrounding structures. The submission indicated that tofacitinib is intended to be used following inadequate response to methotrexate (MTX) and disease modifying anti-rheumatic drugs (DMARDs) as second line therapy. Tofacitinib is a Janus-associated kinase (JAK) inhibitor and is orally administered.

- 4.2 The clinical place of tofacitinib in the treatment for RA is yet to be fully established. Current second line therapies (T-cell co-stimulation modulators, TNF-inhibitors, chimeric anti-CD20 monoclonal antibody, IL-6 inhibitor) cover a variety of cell targets and have well-established efficacy and safety profiles in RA.

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

5 Comparator

- 5.1 The submission nominated adalimumab (a TNF-inhibitor) as the main comparator.
- 5.2 Given the concerns that were raised during the TGA registration process regarding the clinical place of tofacitinib for the treatment of RA, the evaluation identified that it is unlikely that adalimumab is the appropriate comparator. The ESC agreed with this view. While the submission claimed that a clinical need existed for tofacitinib due to its oral administration and the novel mechanism of action, these characteristics are unlikely to be sufficient reason to consider this drug as an appropriate second line therapy. In the recent update to the European League against Rheumatism (EULAR) guidelines (Smolen 2014), tofacitinib was recommended as treatment following failure of at least one bDMARD. In addition, UptoDate[®] recommended the use of tofacitinib following resistance to two TNF inhibitors¹. Given the likelihood for use in the third line setting, the evaluation suggested that a comparison with rituximab, also currently PBS listed for severe active rheumatoid arthritis, would have been potentially beneficial. The submission included one placebo controlled trial (Study 1032) investigating tofacitinib in patients that have failed a TNF inhibitor.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The rheumatologist presenting at the hearing addressed the clinical positioning of tofacitinib in the treatment algorithm for RA, tofacitinib's relative effect on disease modification and tofacitinib's comparative safety. The clinician's view was that there is a clinical need for further second line treatments to be available in RA. The clinician emphasised the importance of early treatment and an association with better health outcomes with early treatment. In terms of structural preservation, the clinician noted the lack of statistical significance in the results of the trials presented in the submission regarding tofacitinib 5 mg in terms of its effect on disease modification outcome measures but maintained that there is nonetheless a positive benefit achieved with the 5 mg dose and is comparable with other bDMARDs. With respect to comparative safety, the clinician contended that the adverse event profile of tofacitinib is comparable to existing bDMARDs.

¹ Available from: http://www.uptodate.com/contents/treatment-of-rheumatoid-arthritis-resistant-to-initial-dmard-therapy-in-adults?source=search_result&search=tofacitinib&selectedTitle=4~19. Last accessed: 15 December 2014.

6.2 The PBAC considered that the hearing was informative.

Consumer comments

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

Clinical trials

6.4 The submission was based on two head-to-head trials comparing tofacitinib to adalimumab in combination with MTX (Study 1064, n=717) or as monotherapy (Study 1035, n=386). In addition, an indirect comparison of tofacitinib versus adalimumab was included in the main body of the submission. Results from the indirect comparison were considered to be supplementary given the availability of direct evidence.

6.5 Details of the head to head trials presented in the submission are provided in the following table.

Head to head trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Study 1064	Phase 3 Randomized, Double-Blind, Active Comparator, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background Methotrexate	2012
van Vollenhoven RF	ORAL Standard Investigators. Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis	<i>The New England Journal of Medicine</i> 2012; 367(6):508-519
Study 1035	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Active Comparator, Multicenter Study to Compare 5 Dose Regimens of CP-690,550 and Adalimumab versus Placebo, Administered for 6 Months in the Treatment of Subjects with Active Rheumatoid Arthritis.	2010
Fleischmann R	Phase IIb Dose-Ranging Study of the Oral JAK Inhibitor Tofacitinib (CP-690,550) or Adalimumab Monotherapy Versus Placebo in Patients with Active Rheumatoid Arthritis With an Inadequate Response to Disease-Modifying Antirheumatic Drugs.	<i>Arthritis & Rheumatism</i> 2012; 64(3):617-629

Source: Table 4, pB.17 of the submission

6.6 The key features of the direct randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration of direct comparison	Risk of bias	Patient population	Primary objective(s)
Study 1064	717	R, DB, AC, MC Phase 3, 12 months	Low	RA with active disease (≥6 tender/painful joints on motion and ≥6	Tofa 5mg & 10mg bd vs PBO (+MTX): ACR20 at 6 months; HAQ-DI at 3 months; DAS28-4<2.6 at 6 months;

Trial	N	Design/ duration of direct comparison	Risk of bias	Patient population	Primary objective(s)
Study 1035	386	R, DB, AC, MC, Phase 2b	Low	swollen joints) and elevations in acute phase reactant tests.	safety and tolerability over 12 months Characterise the dose response of tofacitinib over the range of 1-15mg bd on ACR20 response at 12 weeks

Abbreviations: AC = active control; Ada = adalimumab ACR = American College of Rheumatology; bd = twice a day; DAS = disease activity score; DB = double blind; HAQ-DI = Health Assessment Questionnaire-Disability Index; MC = multicentre; PBO = placebo; q2w: once a fortnight; R = randomised; Tofa = tofacitinib; Source: Table 5, pB.18 of the submission

Source: compiled during the evaluation

- 6.7 The head to head trials were not designed or powered to definitively compare tofacitinib and adalimumab in severe active RA. Although both trials were 12 months duration, the direct comparison was limited to 3 months in Study 1035.
- 6.8 A comparison between the trial eligibility criteria and the proposed PBS restriction showed that the proposed PBS restriction targeted patients of greater RA severity (swollen/tender joint count and measures of C-reactive protein) when compared to the eligibility criteria used in the randomised trials (Study 1064, Study 1035).
- 6.9 In terms of prior treatment, the requested PBS restriction specified the failure of intensive treatment with DMARDs (MTX \geq 20 mg/week or DMARD for at least 3 continuous months) prior to the commencement of tofacitinib, whereas the head to head trials only required minimal treatment failure (inadequate response to MTX 7-25 mg/week for \geq 6 weeks: Study 1064; treatment failure with \geq 1 DMARD: Study 1035). Additionally, participants were excluded from both trials if they had discontinued any previous TNF-inhibitor therapy for lack of efficacy or adverse events. Given the eligibility criteria for prior DMARD and bDMARD treatment in the head to head trials it would be expected that the utilisation of these agents would be reduced compared to usage in the requested PBS population.

Comparative effectiveness

- 6.10 Results of the American College of Rheumatology (ACR) response rates (ACR20, ACR50 and ACR70 at 3 months) from the direct randomised trials and the meta-analyses are presented in the table below. The pooled results indicated a statistically significant advantage for tofacitinib 5 mg compared to adalimumab 40 mg for ACR50 at 3 months.

Results of ACR20, ACR50 and ACR70 response rates at 3 months

Outcome	Trial	Tofa 5mg, n/N (%)	Ada 40mg, n/N(%)	RD (95% CI)	RR (95% CI)
ACR20	Study 1065	119/196 (60.7)	112/199 (56.3)	0.04 (-0.05, 0.14)	1.08 (0.91, 1.27)
	Study 1035	30/49 (61.2)	21/53 (39.6)	0.22 (0.03, 0.41)	1.55 (1.04, 2.31+)
	Meta-analysis			0.11 (-0.05, 0.27) I ² = 60%	1.23 (0.88, 1.73) I ² = 62%
ACR50	Study 1065	67/196 (34.2)	47/199 (23.6)	0.11 (0.02, 0.19)	1.45 (1.05, 1.99)
	Study 1035	19/49 (38.8)	11/53 (20.8)	0.18 (0.01, 0.35)	1.87 (0.99, 3.52)
	Meta-analysis			0.12 (0.04, 0.20) I ² = 0%	1.52 (1.15, 2.02) I ² = 0%
ACR70	Study 1065	24/196 (12.2)	17/199 (8.5)	0.04 (-0.02, 0.10)	1.43 (0.80, 2.58)
	Study 1035	7/49 (14.3)	2/53 (3.8)	0.11 (-0.01, 0.22)	3.79 (0.83, 17.36)
	Meta-analysis			0.05 (-0.00, 0.11) I ² = 11%	1.79 (0.80, 4.01) I ² = 27%

Figures in bold indicate results that are statistically significant. Abbreviations: ACR = American College of Rheumatology; Ada = adalimumab; Tofa = tofacitinib; CI = confidence interval; RD = risk difference; RR = relative risk. Source: Table 42 43 & 44, ppB.122-B.124 and Table 47, pB.129-B.130 of the submission

- 6.11 Results of the meta-analyses and indirect comparison for ACR response at 3 months are presented in the table below. No statistically significant difference was observed for tofacitinib 5 mg and adalimumab 40 mg for ACR20 and ACR50 response at 3 months. The high level of statistical heterogeneity in the meta-analyses of the tofacitinib trials and variation in placebo response rates across the trials compromised the validity of the indirect comparison.

Summary of results for the indirect comparison for ACR response at 3 months across the combination and monotherapy trials.

Outcome	Tofacitinib, n/N (%)	Placebo, n/N (%)	Adalimumab, n/N (%)	RD (95% CI)	RR (95% CI)
ACR20 at 3 months	743/1256 (59.2)	196/745 (26.3)	-	0.38 (0.29, 0.48) I ² = 79%	2.30 (1.89, 2.80) I ² = 51%
	-	265/1121 (23.6)	720/1393 (51.7)	0.27 (0.22, 0.33) I ² = 47%	2.07 (1.75, 2.44) I ² = 46%
	Indirect comparison			0.11 (-0.00, 0.22)	1.11 (0.86, 1.44)
ACR50 at 3 months	404/1256 (32.2)	75/745 (10.1)	-	0.26 (0.19, 0.32) I ² = 66%	3.25 (2.56, 4.13) I ² = 6%
	-	81/1065 (7.6)	33/1234 (26.9)	0.19 (0.16, 0.22) I ² = 0%	3.38 (2.68, 4.24) I ² = 0%
	Indirect comparison			0.06 (-0.00, 0.13)	0.96 (0.69, 1.34)

Figures in bold indicate results that are statistically significant
Abbreviations: ACR = American College of Rheumatology; CI = confidence

- 6.12 A comparison between tofacitinib and placebo in patients who have failed TNF-inhibitor therapy is presented in the table below. Results for ACR response at 3 months indicate statistically significant differences in favour of tofacitinib 5 mg using both ACR20 and ACR50 response measures.

ACR 20 and ACR 50 response rates at 3 months (Study 1032)

Outcome	Tofa 5mg, n/N (%)	Placebo, n/N(%)	RD (95% CI)	RR (95% CI)
ACR20 at 3 months	55/132 (41.7)	32/131 (24.4)	0.17 (0.06, 0.28)	1.71 (1.19, 2.45)
ACR50 at 3 months	35/132 (26.5)	11/131 (8.4)	0.18 (0.09, 0.27)	3.16 (1.68, 5.95)

Figures in bold indicate results that are statistically significant
Abbreviations: ACR = American College of Rheumatology; CI = confidence interval; RD = risk difference; RR = relative risk;

Tofa = tofacitinib. Source: Table 54, pB.144 and Table 57, pB.149 of the submission

- 6.13 The ESC noted a published study by Van der Heijde et al (2013)² where tofacitinib 5 mg twice daily and 10 mg twice was assessed for efficacy against placebo (using ACR20 response rates). Results indicated statistically significant response rates for both tofacitinib 5 mg and 10 mg (51.5% and 61.8% respectively) over placebo (25.3%). However, with respect to joint damage, the ESC also noted that the results for radiographic progression and structural preservation in terms of total SHS (Sharp/van der Heijde score) were not statistically significant for tofacitinib 5 mg twice daily but were for the 10 mg twice daily dose. As the submission proposes only listing the 5 mg dose, the ESC advised that further consideration of the importance of joint preservation would be needed.

Comparative harms

- 6.14 A summary of the key overall safety outcomes at 3 months (meta-analysis of Study 1035 and Study 1064) and 6 months (Study 1064) is presented in the table below. No statistically significant differences were observed across the overall safety outcomes at 3 months. For the six month results from Study 1064, a statistically significant difference in favour of adalimumab was demonstrated for patients with serious adverse events.

Key overall safety outcomes at 3 and 6 months

	Study 1035 and Study 1064: 3 months		Study 1064: 6 months	
	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Patients with AEs	1.00 (0.84, 1.18)	0.00 (-0.09, 0.09)	1.02 (0.87, 1.19)	0.01 (-0.08, 0.10)
Patients with serious AEs	1.73 (0.42, 7.08)	0.01 (-0.04, 0.06)	2.00 (1.00, 4.02)	0.05 (0.00, 0.11)
Patients with severe AEs	2.17 (0.84, 5.59)	0.02 (-0.02, 0.06)	0.93 (0.45, 1.93)	-0.00 (-0.05, 0.04)
Discontinuation due to AEs	0.60 (0.06, 6.35)	-0.02 (-0.12, 0.07)	1.00 (0.55, 1.83)	0.00 (-0.06, 0.06)
Dose reduction or temporary discontinuation due to AEs	1.12 (0.58, 2.17)	0.01 (-0.02, 0.05)	1.35 (0.81, 2.23)	0.04 (-0.03, 0.10)

Figures in bold indicate results that are statistically significant. Abbreviations: AEs = adverse events; CI = confidence interval; RD = risk difference; RR = relative risk. Source: Table 64 and Table 65, ppB.160-B.162 of the submission.

- 6.15 In regard to adverse events of special interest, changes in haemoglobin were slightly greater for adalimumab compared to tofacitinib while increases in liver enzymes were similar across the two drugs. While the submission did not report results of any statistical analyses for change in lipid parameters, the trial report for Study 1064 indicated that increases for tofacitinib were statistically significantly greater than adalimumab (see table below and benefits/harms table in para 6.17).

Statistical analysis of change from baseline in lipid parameters (Study 1064)

Lipid parameter		Tofacitinib 5mg		Adalimumab 40mg		MD, 95% CI
		n	LS mean (SE)	n	LS Mean (SE)	
Total cholesterol (mg/dL)	Month 1	192	9.90 (1.10)	196	3.75 (1.09)	6.15 (3.26, 9.04)
	Month 3	185	11.05 (1.11)	190	3.36 (1.10)	7.69 (4.76, 10.62)

² Van der Heijde, D et al. Tofacitinib (CP-690,550) in Patients With Rheumatoid Arthritis Receiving Methotrexate, *Arthritis & Rheumatism*. 2013;65(3):559-570

Lipid parameter		Tofacitinib 5mg		Adalimumab 40mg		MD, 95% CI
		n	LS mean (SE)	n	LS Mean (SE)	
HDL-C (mg/dL)	Month 6	127	11.70 (1.25)	126	1.30 (1.25)	10.41 (7.06, 13.76)
	Month 1	192	12.03 (1.46)	196	4.62 (1.45)	7.41 (3.57, 11.25)
	Month 3	185	12.17 (1.48)	190	5.64 (1.47)	6.52 (2.64, 10.41)
	Month 6	126	10.87 (1.67)	126	2.39 (1.67)	8.47 (4.01, 12.93)
LDL-C (mg/dL)	Month 1	189	10.97 (1.91)	194	4.13 (1.89)	6.84 (1.82, 11.85)
	Month 3	181	12.18 (1.94)	187	3.62 (1.91)	8.56 (3.48, 13.64)
	Month 6	125	14.16 (2.15)	125	1.76 (2.13)	12.40 (6.70, 18.11)

Figures in bold indicate results that are statistically significant

Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein; LS = least square; MD = mean difference; SE = standard error.

Source: Table 14.3.4.1.10.7; Table 14.3.4.1.11.5, Table 14.3.4.1.12.5 of the clinical study report for Study 1064

- 6.16 In the extended assessment of comparative harms, the periodic safety update report (PSUR) listed the following important identified risks for tofacitinib: opportunistic infections, lymphoma and malignancy, gastrointestinal perforations, alterations in liver enzymes and non-melanoma skin cancer. Similar adverse events have been reported with existing bDMARDs. Currently, there is insufficient evidence to determine whether any relative differences in adverse events are apparent across the therapies.

Benefits/harms

- 6.17 A summary of the comparative benefits and harms for tofacitinib versus adalimumab is presented in the table below.

Summary of comparative benefits and harms for tofacitinib and adalimumab

Trial	Tofacitinib	Adalimumab	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				Tofacitinib	Adalimumab		
Benefits							
ACR20 at 3 months							
Meta-analysis	149/245	133/252	1.23 (0.88, 1.73)	60.8	52.8	0.11 (-0.05, 0.27)	
ACR50 at 3 months							
Meta-analysis	86/245	58/252	1.52 (1.15, 2.02)	35.1	23.0	0.12 (0.04, 0.20)	
ACR70 at 3 months							
Meta-analysis	31/245	19/252	1.79 (0.80, 4.01)	12.7	7.5	0.05 (-0.00, 0.11)	
Harms: change from baseline in lipid parameters at month 6							
	Tofacitinib			Adalimumab			Mean difference: Tofacitinib vs Adalimumab (95% CI)
	n	LS mean Δ baseline	SE	n	LS mean Δ baseline	SE	
HDL-C (mg/dL)							
Study 1064	126	10.87	1.67	126	2.39	1.67	8.47 (4.01, 12.93)
LDL-C (mg/dL)							
Study 1064	125	14.16	2.15	125	1.76	2.13	12.40 (6.70, 18.11)

Abbreviations: American College of Rheumatology = ACR; HDL = high density lipoprotein; LDL = low density lipoprotein; LS = least square; MD = mean difference; PBO = placebo SE = standard error; RD = risk difference; RR = risk ratio. Source: Compiled during the evaluation.

- 6.18 On the basis of direct evidence presented by the submission, for every 100 patients treated with tofacitinib in comparison to adalimumab:
- Approximately 12 additional patients would have ACR50 response at 3 months.

- No significant differences were observed for ACR20 and ACR70 response at 3 months.
- 6.19 On the basis of direct evidence presented by the submission, the comparison of tofacitinib and adalimumab resulted in:
- Approximately a 8.47 mg/dL increase in high density lipoprotein cholesterol (HDL-C) over a 6 month period.
 - Approximately a 12.40 mg/dL increase in low density lipoprotein cholesterol (LDL-C) over a 6 month period.
 - The submission claimed the clinical significance of differences in lipid levels was uncertain since higher LDL-C levels are known to increase cardiovascular risk and higher HDL-C levels have a cardio-protective effect.
 - Increased risk with either agent of opportunistic infection, lymphoma and malignancy, elevated liver function tests and anaemia, which will be further evaluated for tofacitinib through a planned pharmacovigilance study.

Clinical claim

- 6.20 The submission described tofacitinib as non-inferior to adalimumab with regard to efficacy and safety.
- 6.21 The claim of non-inferior efficacy was adequately supported by the evidence. No significant differences in ACR response at 3 months (ACR20, ACR70) was observed in the meta-analysis of the direct randomised trials. Results from the indirect comparison were considered to support the efficacy claim, although the analysis was compromised by a high level of statistical heterogeneity and variation of placebo response rates across the trials. As noted earlier, with respect to joint damage, the ESC observed that the results for radiographic progression and structural preservation in terms of total SHS (Sharp/van der Heijde score) were not statistically significant for tofacitinib 5 mg twice daily but were for the 10 mg twice daily dose. As the submission proposes only listing the 5 mg dose, the ESC advised that comparative efficacy measured by extent of joint preservation was not adequately supported.
- 6.22 The claim of non-inferior safety was not adequately supported by the evidence. Statistically significant increases in total cholesterol, LDL-C and HDL-C were reported for the comparison of tofacitinib 5 mg and adalimumab 40 mg in Study 1064. While it is accepted that increases to HDL-C are associated with cardio-protective effects, there are potential long term cardiovascular risks associated with elevated LDL-C and total cholesterol. The ESC considered that relative prevalence and severity of other adverse events, such as opportunistic infection cannot be accurately determined from the data presented.

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

Economic analysis

- 6.23 The submission presented a cost-minimisation analysis against adalimumab.

- 6.24 The equi-effective doses were estimated as tofacitinib 5 mg twice a day and adalimumab 40 mg every fortnight. The doses were consistent with the treatment regimens used in the head to head and indirect comparisons.
- 6.25 The submission proposed an effective price of \$ [REDACTED] for tofacitinib 5 mg. The requested effective price is the same as that for etanercept, given the sponsor's knowledge of the special pricing arrangement (SPA) with the Commonwealth ([REDACTED]% rebate, post adjustment for average co-payments).
- 6.26 The suitability of the CMA was compromised by the following factors:
- Non-inferiority in terms of comparative safety was not adequately supported by the evidence, given the significant increases in lipid parameters and the limited long term safety profile for tofacitinib.
 - The cost minimisation approach was reliant upon the acceptance of adalimumab as the appropriate main comparator. As noted above, current treatment guidelines for RA (Smolen 2014, UptoDate[®]) designate tofacitinib as a third line therapy following bDMARD/TNF-inhibitor failure (refer to section 4 and 5 above).
- 6.27 The submission assumed cost equivalence between administration (adalimumab: subcutaneous injection) and adverse event costs (tofacitinib: hypercholesterolaemia), with no adjustments being applied in the CMA or financial estimates. This conclusion was unjustified as no quantitative analysis was presented to determine whether costs relating from hypercholesterolemia were equivalent to administration costs. The ESC agreed with the evaluation that it was unreasonable to assume cost-equivalence, given the apparent differences in characteristics of resource use:
- Costs resulting from hypercholesterolemia (monitoring, statin treatment, costs resulting from cardiovascular morbidity) are likely to be ongoing as treatment with tofacitinib is intended to be long term.
 - Costs of monitoring for other serious adverse effects (e.g. full blood count, skin checks, and of treating serious infections and malignancies), may vary between the agents and this cannot be assessed without knowledge of the relevant prevalence or severity of these events.
 - For the majority of bDMARDs, administration costs are likely to be relevant during the initiation of treatment where a nurse educator may be involved. Ongoing assistance with subcutaneous administration would only be expected in the minority of circumstances.
- 6.28 The ESC noted that although the clinical evidence indicated an equi-effective dose of tofacitinib 5 mg twice daily and adalimumab 40 mg subcutaneously every fortnight, the submission calculated treatment costs based on etanercept. As etanercept is also licensed by the sponsor, the sponsor is aware of the associated special pricing arrangements. According to the therapeutic relativity sheet, adalimumab for use in RA was recommended for listing on a cost minimisation basis versus etanercept with the equi-effective doses being 40 mg adalimumab every second week = 25 mg etanercept twice weekly. By inference, the submission concluded equi-effective doses of tofacitinib 5 mg twice daily and etanercept 50 mg subcutaneously every second week³. Although this approach was reasonable, the ESC agreed with the

³ In practice etanercept is most commonly used as a 50 mg subcutaneous injection once weekly as opposed to 25 mg twice weekly

evaluation that the clinical evidence may not adequately support a claim of non-inferiority for safety so a basis for performing a cost-minimisation analysis was yet to be clearly established.

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

Drug cost/patient/year

6.29 The drug cost/patient/year was estimated to be \$ [REDACTED]. Tofacitinib is intended to be long term treatment. Drug cost/patient/year is based on an effective daily treatment cost of \$ [REDACTED] over 365.25 days.

Estimated PBS usage & financial implications

6.30 The submission used a market share approach to estimate the utilisation and financial implications associated with the requested PBS listing of tofacitinib on the PBS for severe rheumatoid arthritis (RA).

Estimated use and financial implications of listing tofacitinib in the first five years

			Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use							
Tofacitinib	Treatment months (market share, %)		[REDACTED] ([REDACTED]%)	[REDACTED] ([REDACTED]%)	[REDACTED] ([REDACTED]%)	[REDACTED] ([REDACTED]%)	[REDACTED] ([REDACTED]%)
	Net costs		\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
bDMARDs substituted by tofacitinib	Treatment months (market share, %)	Etanercept	61,986 (22.5%)	65,889 (21.7%)	70,298 (21.2%)	74,586 (20.8%)	78,477 (20.3%)
		Adalimumab	69,536 (25.2%)	74,195 (24.5%)	79,361 (24.0%)	84,405 (23.5%)	89,052 (23.1%)
		Other bDMARDs	125,988 (45.7%)	137,453 (45.3%)	149,172 (45.1%)	160,830 (44.9%)	172,289 (44.6%)
	Net costs		\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated net cost to PBS/RPBS							
Net cost to PBS/RPBS			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: bDMARDs = biological disease modifying antirheumatic drugs. Source: Table 9, pE12 of the submission

6.31 Based on an analysis of online Medicare data for currently listed biological disease modifying anti-rheumatic drugs (bDMARDs) (October 2009 to September 2014), the submission noted an overall steady, near linear increase in annual services ($y = 1725.8x + 21467$). It was assumed that future market growth was to continue in a linear fashion with historical market growth. The submission assumed that the listing of tofacitinib would not add to market growth with a neutral effect upon the overall budget, with direct substitution for other bDMARDs at the effective price of \$ [REDACTED] per treatment month. DUSC agreed with the commentary that the submission’s approach to the calculation of the bDMARD market was reasonable, but considered there is likely to be additional market growth due to the addition of an oral treatment for RA.

6.32 DUSC noted the sensitivity analyses included in the commentary of a 5% and 10% expansion of the market, and that under the assumption of a 10% market expansion, the submission estimated net cost to the PBS of \$30 – \$60 million in Year 1 and \$30 – \$60 million in Year 5. DUSC commented this represents a large increase in the cost to the PBS.

- 6.33 DUSC considered the estimates presented in the submission to be underestimated for the following reasons:
- There is likely to be additional market growth due to the addition of an oral treatment in the bDMARD phase of the treatment for rheumatoid arthritis (RA).
 - The submission's estimate of 6% uptake within the RA market is a large underestimate.
 - The price requested by the sponsor may not be reasonable as tofacitinib is not disease-modifying in the same way as the biological disease-modifying anti-rheumatic drugs. DUSC advised that it is not reasonable to offset the costs of increased statin use with reduced injection costs due to oral treatment.
 - The costs of treating infections resulting from tofacitinib use should be included in the estimates.

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

7 PBAC Outcome

- 7.1 The PBAC recommended listing tofacitinib as an Authority Required listing for the treatment of severe active rheumatoid arthritis in patients meeting certain criteria on a cost-minimisation basis with adalimumab. The equi-effective doses were determined to be tofacitinib 5 mg twice daily and adalimumab 40 mg subcutaneously every fortnight.
- 7.2 The submission's clinical positioning of tofacitinib as an alternative second line therapy to existing PBS-listed bDMARDs was in line with the final TGA registered indication but was in contrast to the TGA's Delegate's proposal to register tofacitinib to third-line therapy and recent updates to the European League against Rheumatism (EULAR) (Smolen 2014) and UptoDate[®] guidelines which recommend using tofacitinib as third line therapy. The PBAC noted that tofacitinib belonged to a new class of bDMARDs, being a Janus kinase (JAK) selective inhibitor and would be the first oral bDMARD therapy. The PBAC considered that given that the final TGA registered indication permits use of tofacitinib as second line therapy, the submission's nominated main comparator of adalimumab was considered to be acceptable.
- 7.3 The PBAC noted the potential applicability issues concerning the characteristics of the trial subjects and the proposed PBS population for treatment as identified by the evaluation and that the trials presented in the submission were not designed or powered to definitively compare tofacitinib and adalimumab in severe active rheumatoid arthritis. However, the PBAC noted that the trial evidence contained head-to-head trials comparing tofacitinib to adalimumab in combination with methotrexate (Study 1064, n=717) or as monotherapy (Study 1035, n=386) and that there was a reasonably large enough study sample size for the PBAC to consider the clinical trial data to be sufficiently reliable.
- 7.4 Pooled results of the American College of Rheumatology (ACR) response rates (ACR20, ACR50 and ACR70 at 3 months) from the direct randomised head to head trials and the meta-analyses of these trials indicated a statistically significant

advantage for tofacitinib 5 mg compared to adalimumab 40 mg for ACR50 at 3 months. In contrast, results of the indirect comparison for ACR response at 3 months showed no statistically significant difference observed for tofacitinib 5 mg and adalimumab 40 mg for ACR20 and ACR50 response at 3 months. The PBAC noted the high level of statistical heterogeneity in the meta-analyses of the tofacitinib trials and variation in placebo response rates across the trials may have reduced the reliability of the indirect comparison. Based on these results, the PBAC accepted the submission's claim of non-inferiority in terms of comparative efficacy to adalimumab using ACR outcome measures.

- 7.5 In relation to concerns raised by the evaluation and ESC regarding tofacitinib 5 mg's ability to reduce or prevent radiographic disease progression or maintain structural preservation, the PBAC was unclear on the reliability and accuracy of the Sharp/van der Heijde scoring system to be a predictor of disease modification achieved by a drug. The PBAC noted the clinician presenting in the hearing was of the view that whilst the 5 mg tofacitinib dose did not reach statistical significance in terms of effect on radiographic disease progression and structural preservation in clinical trials, there are signs of a positive effect in this regard and that tofacitinib is comparable to other bDMARDs in this regard. The PBAC recalled that its previous considerations of bDMARD submissions for severe active rheumatoid arthritis have predominantly relied on ACR response rate outcomes and so on balance, although tofacitinib 5 mg did not clearly establish an effect on disease modification, the PBAC was of the view that this was not a strong enough reason to reject the proposed listing.
- 7.6 In terms of comparative safety, the PBAC noted that no statistically significant differences were observed across the overall safety outcomes at 3 months. For the six month results from Study 1064, a statistically significant difference in favour of adalimumab was demonstrated for patients with serious adverse events. Tofacitinib also appeared to result in an increased risk of infections, including chest infections and cellulitis. While the submission did not report results of any statistical analyses for change in lipid parameters, the PBAC noted that the trial report for Study 1064 indicated that increases for tofacitinib were statistically significantly greater than adalimumab. Therefore, the PBAC considered that the claim of non-inferior safety was not fully supported by the evidence. This had resulting consequences for the economic analysis.
- 7.7 The PBAC noted that the submission's cost-minimisation analysis of tofacitinib against adalimumab assumed cost equivalence between administration (adalimumab would incur greater administration costs due to its subcutaneous injection route of administration) and adverse event costs (tofacitinib appeared to have higher rates of hypercholesterolaemia) despite a lack of quantitative analysis demonstrating that costs arising from increased hypercholesterolemia were countered equally by reduced administration costs for tofacitinib. In line with the PBAC's March 2010 consideration of tocilizumab for rheumatoid arthritis, given the evidence regarding statistically significantly greater changes in lipid parameters resulting from tofacitinib treatment, the PBAC considered that the inclusion of hypercholesterolemia management costs for a proportion of patients would be appropriate. The PBAC further did not recommend a cost-offset be applied for reduced administration costs, as the PBAC agreed that assistance with subcutaneous administration would only be expected in the minority of circumstances.

- 7.8 Equi-effective doses of tofacitinib 5 mg twice daily and adalimumab 40 mg subcutaneously every fortnight were accepted by the PBAC.
- 7.9 The PBAC agreed with the DUSC advice that the submission's estimates of the financial implications of listing tofacitinib, particularly in relation to the estimate of 6% uptake within the RA market. The PBAC's view was that tofacitinib's oral route of administration was likely to make this uptake rate higher than predicted by the submission. This was not expected to have a financial implication based on a cost-minimisation listing. However, the PBAC agreed with the DUSC advice that the oral route of administration may have the potential of growing the RA market and so recommended DUSC review tofacitinib utilisation following 12 months of listing to confirm whether the RA market had grown beyond historical trends. DUSC had also advised that the costs of increased infections with tofacitinib should be accounted for in the estimates but the PBAC agreed that this would be difficult to estimate, as current RA treatments also cause infections.
- 7.10 Although the submission had requested a 'Grandfathering' clause in the proposed PBS restriction, the PBAC noted that the number and source of such patients (e.g. private treatment, hospital in-patient treatment, sponsor access program, clinical trials) had not been adequately justified by the sponsor. Therefore, unless there was a clear identification of such patients by the sponsor, the PBAC was not supportive of a grandfather clause.
- 7.11 The PBAC further noted that existing special pricing arrangements apply to existing bDMARDs in the treatment of rheumatoid arthritis and that it would be suitable for the same arrangements to apply to tofacitinib.
- 7.12 Consistent with a cost-minimisation recommendation, the PBAC agreed that the listing for tofacitinib should target the same patient population as the current restrictions for the existing bDMARDs for severe active RA and that the interchangeability rules (swapping criteria) should be retained. This means that within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised bDMARD more than once. Once a patient has either failed or ceased to respond to three therapies, they are deemed to have completed a treatment cycle and they must have a minimum 5 year break.
- 7.13 The PBAC noted the correspondence from the Australian Rheumatology Association (ARA) expressing concern over ambiguity in the use of the term 'specialist physician with expertise in the management of rheumatoid arthritis in the TGA registered indication and potential use in any proposed PBS restriction. In reply to this, the sponsor provided reassurance that it did not intend for tofacitinib to be available to a wider prescriber group than that currently available for the existing bDMARDs for RA. The PBAC agreed that it would be reasonable to ensure that the prescriber types for tofacitinib and existing PBS-listed bDMARDs used in RA aligned.
- 7.14 Advice to the Minister under subsection 101(3BA) of the Act
In accordance with subsection 101(3BA) of the Act the PBAC advised that it is of the opinion that, on the basis of the material available to it at its March 2015 meeting, tofacitinib should not be treated as interchangeable on an individual patient basis

with any other drugs.

7.15 The PBAC advised that tofacitinib is not suitable for prescribing by nurse practitioners.

7.16 The PBAC recommended that the Safety Net 20 Day Rule should apply to tofacitinib.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Proprietary Name and Manufacturer
TOFACITINIB Tablet 5 mg, 56	TBA	TBA	TBA	Xeljanz NV

TBA – to be announced

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	Severe active
Condition:	rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	To be finalised
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – (method to be advised)
Treatment criteria:	To be finalised
Clinical criteria:	To be finalised
Population criteria:	To be finalised
Prescriber Instructions:	To be finalised
Administrative Advice	To be finalised
Cautions	To be finalised

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

Pfizer Australia welcomes the PBAC recommendation to list tofacitinib on the PBS for rheumatoid arthritis. Tofacitinib is an oral agent with a unique mechanism of action, providing an important new treatment option for Australian patients.