

PUBLIC SUMMARY DOCUMENT

Product: FEBUXOSTAT, tablet, 80 mg, and 120 mg, Adenuric[®]

Sponsor: A. Menarini Australia Pty Ltd

Date of PBAC Consideration: March 2014

1. Purpose of Application

The submission requested an Authority Required (Streamlined) listing for the treatment of chronic gouty arthritis associated with hyperuricaemia.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report, TGA Delegate's Overview, and ACPM outcome were available.

The sponsor informed the PBAC that febuxostat 120 mg was not recommended for registration by the TGA and therefore the PBAC no longer considered the listing of this strength.

Febuxostat 80 mg tablets commenced registration on the Australian Register of Therapeutic Goods on 18 December 2014 and are indicated for the treatment of symptomatic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation) in adults with gout.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)

Chronic gouty arthritis associated with hyperuricaemia.

Note: Febuxostat should be initiated at dose of 80mg once daily. If serum uric acid is $>357\mu\text{mol/L}$ (6mg/dL) after 2-4 weeks, febuxostat 120mg once daily may be considered.

Listing was sought on a cost effectiveness basis with febuxostat compared to allopurinol.

5. Clinical Place for the Proposed Therapy

Gout is a metabolic disorder where clearance of uric acid is impaired leading to hyperuricaemia (although not all patients with hyperuricaemia will have gout). Small crystals of uric acid, form in and around the joints, causing inflammation, pain and swelling.

The submission proposed that febuxostat would be an alternative to allopurinol as the first line treatment for chronic gout. Both drugs are inhibitors of xanthine oxidase.

The PBAC noted while allopurinol is generally used in first line treatment for chronic gout, the PBAC considered that there was a clinical need for a second line alternate agent to treat

chronic gout for patients who cannot continue to use allopurinol due to serious hypersensitivity reactions.

The PBAC also noted the December 2008 NICE technology appraisal guidance¹ for “*Febuxostat for the management of hyperuricaemia in people with gout*” which defined intolerance of allopurinol as adverse effects that are sufficiently severe to warrant discontinuation of allopurinol, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation. The PBAC considered that an allopurinol-intolerant population consistent with the definition used in the NICE guidance may be an appropriate basis to define a second-line treatment setting for febuxostat.

6. Comparator

The nominated comparator was allopurinol. The PBAC considered this to be the appropriate comparator for the requested treatment setting.

7. Clinical Trials

The PBAC noted that the submission nominated two head to head randomised control trials (RCTs), APEX and FACT as the primary evidence, where both trials included a fixed dose allopurinol control arm.

The submission nominated EXCEL and CONFIRMS as supplementary evidence on the grounds that these trials were more selective in their recruitment, had a large proportion of subjects recruited from other completed febuxostat trials. The PBAC noted that the subjects in both these trials were not all febuxostat-treatment naïve, like in FACT or APEX. EXCEL was nominated as supplementary evidence on the basis that it lacked internal validity due to its open label design and significant patient attrition.

The PBAC noted with the exception of EXCEL, that all included trials had a low risk of bias as they were all double blind, randomised, multi-centre RCTs with adequate follow up and low levels of patient attrition. The PBAC noted that EXCEL was potentially associated with high levels of bias due to (i) being open label and (ii) permitting patients to change therapies between month 1 and 6 at the investigator’s discretion. This resulted in very large and uneven cross over between treatment arms (greater than 30% for the febuxostat groups and approximately 60% for allopurinol). However, it was noted that EXCEL was the only trial with more than one year’s follow up.

¹ <http://publications.nice.org.uk/febuxostat-for-the-management-of-hyperuricaemia-in-people-with-gout-ta164/guidance>

Details of the trials and associated reports presented in the submission are shown in the table below.

Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials		
APEX	A phase II, randomized, multicentre, allopurinol and placebo-controlled study assessing the safety and efficacy of oral febuxostat in subjects with gout	21 September 2004
	Schumacher, H, et al. "Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial."	Arthritis and rheumatism, 2008: Nov 15;59 (11):1540-8.
	Wortmann, R, P Macdonald, B Hunt, and R Jackson. "Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials."	Clin Ther, 2010: Dec; 32(14):2386-97.
	Chohan, S, M Becker, P Macdonald, S Chefo, and R Jackson. "Women with gout: Efficacy and safety of urate-lowering with febuxostat and allopurinol."	Arthritis Care Res (Hoboken), 2012: Feb;64(2):256-61.
FACT	A Phase 3, Randomized, Multicenter Study Comparing the Safety and Efficacy of Oral Febuxostat versus Allopurinol in Patients with Gout	8 Sep 2005
	Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout.	N Engl J Med. 2005 Dec 8;353(23):2450-61.
	Wortmann, R, P Macdonald, B Hunt, and R Jackson. "Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials."	Clin Ther, 2010: Dec; 32(14):2386-97.
	Chohan, S, M Becker, P Macdonald, S Chefo, and R Jackson. "Women with gout: Efficacy and safety of urate-lowering with febuxostat and allopurinol."	Arthritis Care Res (Hoboken), 2012: Feb;64(2):256-61.
Supplementary studies		
EXCEL (Extension trial of APEX and FACT)	Allopurinol Versus Febuxostat in Patients Completing the Phase 3 Trials C02-009 and C02-010 (EXCEL).	6 March 2008
	Becker, M, H Schumacher, P MacDonald, E Lloyd, and C Lademacher. "Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout."	J Rheumatol, 2009: Jun;36(6):1273-82. Epub 2009 Mar 13.
	Whelton, A, P MacDonald, S Chefo, and L Gunawardhana. "Preservation of renal function during gout treatment with febuxostat: a quantitative study."	Postgraduate Medicine, 2013: 125(1):106-14.
CONFIRMS (Extension study of EXCEL and FOCUS)	A Phase 3, Randomized, Multicenter, Double-Blind, Allopurinol-Controlled Study Assessing the Safety and Efficacy of Oral Febuxostat in Patients with Gout	27 June 2008

	Becker, M, et al. "The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial."	Arthritis Res Ther, 2010: Apr 6;12(2):R63.
	Becker, M, P MacDonald, B Hunt, and L Gunawardhana. "Treating hyperuricemia of gout: safety and efficacy of febuxostat and allopurinol in older versus younger subjects."	Nucleosides Nucleotides Nucleic Acids, 2011: Dec;30(12):1011-7.
	Jackson, R, B Hunt, and P MacDonald. "The efficacy and safety of febuxostat for urate lowering in gout patients ≥ 65 years of age."	BMC Geriatr, 2012: Mar 21;12:11.
	Wells, A, P MacDonald, S Chefo, and R Jackson. "African American patients with gout: efficacy and safety of febuxostat vs allopurinol."	BMC Musculoskelet Disord., 2012: Feb 9;13:15.
	Wortmann, R, P Macdonald, B Hunt, and R Jackson. "Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials."	Clin Ther, 2010: Dec; 32(14):2386-97.
	Chohan, S, M Becker, P Macdonald, S Chefo, and R Jackson. "Women with gout: Efficacy and safety of urate-lowering with febuxostat and allopurinol."	Arthritis Care Res (Hoboken), 2012: Feb;64(2):256-61.
Kamtani 2011	Kamatani, N, et al. "An allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan."	Journal of Clinical Rheumatology, 2011: 17(4 Suppl 2):S13-8.
Naoyuki 2011	Naoyuki, K, et al. "An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan."	J Clin Rheumatol., 2011: 17(4 Suppl 2):S44-9.

Meta-analyses of direct randomised trials		
Ye et al (2013)	Peng Ye, Shumin Yang, Wenlong Zhang, Qiong Lv; Qingfeng Cheng, Mei Mei, Ting Luo, Lulu Liu, Shumei Chen, and Qifu Li. "Efficacy and Tolerability of Febuxostat in Hyperuricemic Patients With or Without Gout: A Systematic Review and Meta-Analysis."	Clinical Therapeutics, 2013: 35:2 (180-189).
Tayar et al (2012)	Tayar, J, M Lopez-Olivo, and M Suarez-Almazor. "Febuxostat for treating chronic gout."	Cochrane Database of Systematic Reviews 2012, 2012: Issue 11. Art. No.: CD008653. DOI: 10.1002/14651858.CD008653.pub2.

8. Results of Trials

The table below summarises the proportion of patients requiring treatment for a gout flare by time interval across the randomised trials (the only measure of gout flares reported by the trials):

Summary of patients requiring treatment for a gout flare by time interval across the randomised trials (only relevant treatment arms are shown)

Time interval	PBO	FBX80	FBX 120	ALO	FBX 80 vs ALO		FBX 120 vs ALO	
APEX					<i>RD (95%CI)</i>	<i>RR (95%CI)</i>	<i>RD (95%CI)</i>	<i>RR (95%CI)</i>
					<i>NNT[95%CI]^</i>		<i>NNT[95%CI]^</i>	
Day 1 to Week 28	74/134 (55%)	149/262 (57%)	168/269 (62%)	136/268 (51%)	6% (-2%, 15%)	1.12 (0.96, 1.31)	12%(3%, 20%) 7 [5, 33]	1.23 (1.05, 1.42)
During prophylaxis*	29/133 (22%)	75/262 (29%)	101/268 (38%)^P	64/267 (24%)	5%(-3%, 12%)	1.2 (0.9, 1.6)	14%(6%, 21%) 7 [5, 17]	1.6 (1.2, 2.0)
After prophylaxis*	62/133 (47%)	119/262 (45%)	128/268 (48%)	108/267 (40%)	5%(-3.5%, 13%)	1.12 (0.92, 1.37)	7%(-1%, 16%)	1.18 (0.98, 1.43)
FACT								
Day 1 to week 52	NA	163/255 (64%)	179/250 (72%)	163/251 (65%)	-1% (-9%, 7%)	0.98 (0.86, 1.12)	7% (-1.5%, 15%)	1.10 (0.98, 1.25)
During prophylaxis*	NA	56/253 (22%)	90/250 (36%)	52/248 (21%)	1% (-6%, 8%)	1.06 (0.76, 1.47)	15%(7%, 23%) 7 [4, 14]	1.72 (1.29, 2.31)
After prophylaxis*	NA	146/253 (58%)	151/250 (60%)	151/248 (61%)	-3% (-12%, 5%)	0.95 (0.82, 1.10)	-0.5% (-9%, 8%)	0.99 (0.86, 1.14)
CONFIRMS								
Day 1 to Month 6	NA	235/756 (31%)	-	186/755 (25%)	6% (1.9%, 11%) 17 [9, 53]	1.26 (1.07, 1.49)	NA	NA
EXCEL (by initial treatment)								
Overall	NA	221/649 (34%)	122/292 (42%)	35/145 (24%)	10%(1.6%, 17%) 10 [6, 63]	1.41 (1.05, 1.94)	18% (8.3%, 26%) 5 [4, 10]	1.73 (1.27, 2.40)
≤1 year	NA	192/649 (30%)	111/292 (38%)	32/145 (22%)	8%(-0.6%, 15%)	1.34 (0.98, 1.88)	16% (6.8%, 24%) 6 [4, 10]	1.72 (1.24, 2.44)
>1 year	NA	68/425 (16%)	35/174 (20%)	11/45 (24%)	-8%(-23% 3%)	0.65 (0.39, 1.17)	-4%(-20%, 8%)	0.82 (0.47, 1.51)

Italics represent results calculated during the evaluation using StatsDirect (Version 2.8.0)

Bold typography indicates statistically significant results.

The PBAC noted that EXCEL, the only trial providing evidence of longer term follow up (up to 40 months), showed that the incidence of flares and the proportions of patients with a serum uric acid (sUA) level below 6mg/dL were similar by month 40 between febusostat arms and allopurinol in those that remained on treatment.

The table below summarises the change from baseline in primary tophus size from the randomised trials (only reported by APEX, FACT and EXCEL).

Change from baseline in primary tophus size (ITT patients with tophus) across the randomised trials (only relevant treatment arms are shown)

Trial	Visit	PBO		FBX80		FBX120		ALO	
		N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
APEX*	Week 28	21	-52.0 (-62.5, -21.4)	26	-45.6 (-85.9, 3.0)	35	-54.2^P (-100, -16.7)	46	-31.5 (-95.0, 5.6)
	Final [^]	26	-40.3 (-62.5, -16.7)	42	-33.8 (-85.4, 0.0)	50	-42.4 (-90.3, 0)	61	-22.6 (-66.7, 0) ^P
FACT	Week 28	-	-	36	-29.5 (-66.0, 4.1)	28	-49.5^{a†} (-80.8, -34.9)	33	-28.6 (-54.9, 0.0)
	Week 52	-	-	32	83.4 (-100, -15.6)	26	-65.5 (-85.5, -38.9)	30	-49.7 (-96.0, 0.0)
	Final [^]	-	-	50	-51.7 (-100, -8.3)	51	-43.8 (-83.0, 0.0)	44	-39.6 (-65.0, 1.5)
EXCEL ^c	Day 1 [#]	-	-	87	-57 (-100, -22)	34	-52 (-92, 0)	10	-57 (-100, -15)
	Month 12	-	-	80	-82 (-100, -40)	51	-79 (-100, -26)	9	-56 (-100, -16)
	Month 24	-	-	64	-100 (-100, 54)	32	-96 (-100, -25)	4	-87 (-98, -29)
	Month 36	-	-	1	-83 (-83, -83)	0	NR	0	NR
	Final [^]	-	-	107	-96 (-100, -42)	76	-84 (-100, -16)	14	-67 (-100, 0)

Abbreviations: ALO = allopurinol; PBO = placebo; FBX80 = febuxostat 80 mg; FBX120 = febuxostat 120 mg; FBX240 = febuxostat 240 mg; NR=not reported.

Bold typography indicates statistically significant results

* Comparisons between treatment groups were made with a two-way ANOVA with treatment and baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL) as factors.

^a Statistically significant difference in percent change values versus allopurinol 300mg (p≤0.05)

^P Statistically significant difference in percent change values versus placebo (p≤0.05)

[†] Statistically significant difference in percent change values versus febuxostat 120mg (p≤0.05)

[^]at patients' final assessment, which may be before the maximum trial follow up.

[#] Day 1 is the last value from the participants' previous study APEX or FACT.

^c patients by final stable treatment.

The PBAC noted that overall there were no statistically significant differences between any of the active treatment arms in mean change from baseline in number of tophi across the trials.

The table below summarises the proportions of patients attaining serum uric acid (sUA) below 6mg/dl across the direct randomised trials.

Results of proportion of patients attaining sUA<6mg/dl across the direct randomised trials (only relevant treatment arms from the trials are shown)

Trials (follow up duration)	FBX 80 n/N (%)	FBX 120 n /N (%)	ALO 300 ⁺	FBX 80 vs ALO 300+		FBX 120 vs ALO 300+	
				RD (95%CI) NNT[95%CI] [§]	RR (95%CI)	RD (95%CI) NNT [95%CI] [§]	RR (95%CI)
Last 3 visits							
APEX [^]	126/262 (48%)	175/269 (65%)	60/268 (22%)	26% (17%, 35%)* 4[3, 6]	2.15 (1.67, 2.78)	43% (34%, 51.3%) 2 [2,3]	2.91 (2.30, 3.71)
FACT [^]	136/255 (53%)	154/250 (62%)	53/251 (21%)	32% (23%, 41%)* 3[2,15]	2.53 (1.94, 3.29)	41% (32%, 50%)* 2 [2, 3]	2.92 (2.27, 3.79)
At final visit (patient's last sUA on trial) (note for EXCEL this is based on initial treatment assignment, high degree of bias as large numbers of patients taking allopurinol crossed over to FBX treatment)							
APEX	183/253 (72%)	209/265 (79%)	102/263 (39%)	34% (25%, 41%) 3[2, 4]	1.87 (1.58, 2.22)	40% (32%, 47%) 3 [2, 3]	2.03 (1.73, 2.41)
FACT	185/249 (74%)	193/242 (80%)	88/242 (36%)	38% (30%, 46%) 3[2, 3]	2.04 (1.71, 2.46)	44% (35%, 51%) 2 [2,3]	2.19 (1.85, 2.64)
EXCEL [#]	450/636 (71%)	232/283 (82%)	46/141 (33%)	38% (30%, 46%) 3 [2, 3]	2.17 (1.73, 2.79)	49% (40%, 58%) 2 [2, 3]	2.51 (2, 3.24)
CONFIRMS - All pts [^]	507/756 (67%)	-	318/755 (42.1%)	25% (20%, 30%) 4 [3, 5]	1.59 (1.45, 1.76)	-	-
- Renal impairment patients	360/503 (71.6%)	-	212/501 (42.3%)	29% (23%, 35%) 3 [3, 4]	1.69 (1.51, 1.90)	-	-
At week 28							
APEX	122/161 (75.8%)	163/188 (86.7%)	85/208 (41%)	35% (25%, 44%) 3 [2, 4]	1.85 (1.55, 2.24)	46% (37%, 54%) 2 [2, 3]	2.12 (1.8, 2.54)
FACT	133/186 (72%)	130/159 (82%)	84/199 (42%)	29% (20%, 38%) 3 [3, 5]	1.69 (1.41, 2.05)	40% (30%, 48%) 3 [2, 3]	1.94 (1.63, 2.33)
CONFIRMS (26 weeks)	449/596 (75.3%)	-	287/616 (46.6%)	29% (23%, 34%) 3 [3, 4]	1.62 (1.47, 1.78)	-	-
Pooled MH random effects				30%^b (26%, 34%) 3 [3, 4]	1.67^b (1.55, 1.81)	43%^c (37%, 49%) 3 [2, 5]	2.03^c (1.79, 2.30)
At Week 52							
FACT	129/159 (81.1%)	119/145 (82.1%)	70/178 (39%)	42% (32%, 51%) 2 [2, 3]	2.06 (1.69, 2.51)	43% (33%, 52%) 2 [2, 3]	2.09 (1.71, 2.54)
At 3 years							
EXCEL [#]	109/120 (91%)	43/47 (92%)	9/10 (90%)	0% (-19%, 19%)	1.01 (0.81, 1.25)	1% (-18%, 20%)	1.02 (0.81, 1.27)

Abbreviations: ALO 300 = allopurinol 300 mg; FBX 80 = febuxostat 80 mg; FBX 120 = febuxostat 120 mg; pts=patients
Italics represent results calculated during the evaluation using StatsDirect (Version 2.8.0)
Bold typography indicates statistically significant results.

[§] NNT only estimated when the difference is statistically significant

[^] indicates this is a primary outcome from the trial

+ Reduced dose of allopurinol was administered to patients with renal insufficiency at baseline

* 97.5% CI

[#] this is based on initial treatment assignment, high degree of bias as large numbers of patients taking allopurinol crossed over to FBX treatment

^a last value from the previous study (APEX or FACT)

^b Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 2 (P = 0.52); I² = 0%

^c Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%

The PBAC considered that the advantage of a fast reduction in sUA did not translate into benefits over allopurinol for more clinically meaningful outcomes such as flare reduction, tophi resolution or health-related quality of life (HRQoL). Therefore the PBAC did not agree with the submission's assumption that attaining the biological sUA target (<6mg/dL) would lead to clinically meaningful outcomes.

The PBAC observed that with long term treatment, febuxostat appeared to lose its advantage over allopurinol in sUA reduction in the EXCEL trial and that there was a lack of evidence comparing febuxostat and dose escalated allopurinol (which can be administered up to 900mg/day). The PBAC noted that all included trials used a fixed dose of allopurinol of 300mg/day unless the subject had renal impairment.

The PBAC considered that the trials (APEX, FACT, EXCEL, and CONFIRM) presented in the submission for febuxostat versus allopurinol and placebo controls did not support the link between sUA, flares and tophi burden. Although a significantly greater proportion of patients achieved the target sUA level of below 6mg/dL in the febuxostat treatment arms, this difference in sUA level, did not translate into a benefit in flares prevention or tophi burden reduction after 52 weeks. Patients treated with febuxostat 120mg (the dosage producing the biggest sUA level reductions) by contrast also reported a worse quality of life than allopurinol.

The PBAC considered that the trials presented in the submission did not demonstrate any reduction in acute gout attacks or tophi, nor an improvement in quality of life (QoL). The PBAC considered that the clinical data did not show superior effectiveness to allopurinol for patient relevant outcomes.

The PBAC noted in a pooled safety analysis of trials with up to one year follow up, fewer total adverse events were reported by patients treated with febuxostat (80mg or 120mg) compared to patients treated with allopurinol (pooled RR (95%CI): 0.94 (0.89, 0.99) and 0.90 (0.84, 0.96) respectively. There were greater numbers of patients treated with febuxostat 120mg who discontinued treatment due to flares and adverse events compared to allopurinol (RR (95%CI): 3.42 (1.72, 6.81)) and greater number of patients treated with febuxostat 80mg experienced hypertension compared to allopurinol (RR (95%CI) 4.35 (1.25, 15.09) however, this was only evident at 28 weeks and not at 52 weeks.

In regards to longer term safety (up to 3 years EXCEL trial), after adjusting for duration of exposure, which differed dramatically between the treatments arms of the EXCEL trial, adverse events were similar across the febuxostat and allopurinol groups. The total adverse events were 227, 216 and 245 per 100 person years of exposure for patients receiving febuxostat 80mg, 120mg and allopurinol respectively.

The PBAC noted that there were similar incidence of adverse events (such as headache, diarrhoea) and life-threatening idiosyncratic reaction reported with both febuxostat and allopurinol. It was observed that there were a greater number of cardiovascular events with febuxostat treatment but these were not statistically significant. No dose reduction of febuxostat was required in patients with renal impairment, and hypersensitivity syndrome was not observed with febuxostat treatment.

A summary of the comparative benefits and harms for febuxostat versus allopurinol are presented in the table below.

Benefit/harm summary

Outcome	N (4)	RR (95%CI)	Event rate/100 patients/year		Increment	
			FBX80/120	ALO 300 ^a		
Benefits						
Incidence of Gout flares (during trial follow up)						
Week 26 CONFIRMS	80	1511	1.26 (1.07, 1.49)	31 (26 to 37)	25	6(1 to 12)
Week 28 APEX	80	530	1.12 (0.96, 1.31)	57 (49 to 67)	51	Not significant
	120	537	1.23 (1.05, 1.42)	62 (54 to 73)	51	11 (3 to 22)
Week 52 FACT	80	506	0.98 (0.86, 1.12)	65 (55 to 72)	65	Not significant
	120	501	1.10 (0.98, 1.25)	72 (64 to 81)	65	Not significant
Over 36mths EXCEL	80	794	1.41 (1.05, 1.94)	34 (25 to 47)	24	10 (1 to 23)
	120	437	1.73 (1.27, 2.40)	42 (30 to 58)	24	18 (6 to 34)
sUA <6mg/dL at final visit						
Week 26 CONFIRMS	80	1212	1.62 (1.47, 1.78)	75 (69 to 84)	47	28 (22 to 37)
Week 28 APEX	80	369	1.85 (1.55, 2.24)	76 (64 to 92)	41	35 (23 to 51)
	120	396	2.12 (1.8, 2.54)	87 (74 to 104)	41	46 (33 to 63)
Week 52 FACT	80	337	2.06 (1.69, 2.51)	81 (67 to 98)	39	42 (28 to 59)
	120	323	2.09 (1.71, 2.54)	82 (67 to 99)	39	43 (28 to 60)
36 months EXCEL	80	130	1.01 (0.81, 1.25)	91 (73 to 113)	90	Not significant
	120	57	1.02 (0.81, 1.27)	92 (73 to 114)	90	Not significant
Serous AEs (CONFIRMS, APEX, FACT)						
Pooled 26, 28 & 52 weeks	80	2556	0.88 (0.55, 1.42)	4 (3 to 7)	5	Not significant
	120	1041	1.16 (0.70, 1.93)	6 (4 to 10)	5	Not significant
Discontinuations due to AEs (CONFIRMS, APEX and FACT)						
Pooled 26, 28 & 52 weeks	80	2555	1.05 (0.80, 1.39)	7(6 to 10)	7	Not significant
	120	1041	3.42 (1.72, 6.81)	7 (3 to 14)	2	5 (1 to 12)

Source: compiled during the evaluation

^a lower doses of allopurinol 100mg/d (APEX) and 200mg/d (CONFIRMS) were administered to patient with renal impairment

9. Clinical Claim

The submission described febuxostat as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over allopurinol.

The PBAC considered this claim was reasonable in terms of safety, but that the claim of superior comparative effectiveness was not supported by the evidence presented in the submission.

10. Economic Analysis

The submission presented a cost utility consisting of stepped economic evaluation. The submission presented an incremental cost-effectiveness ratio (ICER) for the 80 mg strength in the range of \$15,000-\$45,000 per quality adjusted life year (QALY).

The utility estimates were driven by sUA levels based on the IMS observation study, resulting in the utilities in the model being independent of flares or tophi. The PBAC noted that the range of utilities in both groups of patients was wide and covered worse than death to

full health, for example patients not experiencing a flare had a mean utility value 0.710 (0.683,0.736, range: -0.429 to 1).

The economic evaluation was structured with four alternative fixed dose treatment groups: febuxostat 80 mg daily (FBX80), febuxostat 120 mg daily (FBX120), allopurinol 300 mg daily (ALO300) and placebo. In the event of treatment discontinuation, patients in each of the three “active” treatment groups were assumed to revert to placebo/no treatment. Similar to the trials, no dose escalation of treatment was permitted for either febuxostat or allopurinol. The PBAC considered that the model presented was not representative of clinical practice as there was no option for dose-escalation or trying alternative treatments.

The PBAC noted that the model was driven by several assumptions, all of which favoured febuxostat:

- In the event of treatment discontinuation, patients in each of the three “active” treatment groups were assumed to revert to placebo/no treatment (i.e. there was no consideration of treatment sequencing).
- The dose of allopurinol was fixed at 300mg per day. Although this was consistent with the trials, best clinical practice allows dose escalation to 900mg per day.
- Lowering of sUA was assumed to lead to utility improvements independently of flares, which were assigned their own disutility. This was considered inappropriate as gout is generally asymptomatic in absence of flare or tophi.
- The probability of gout flares was assumed to increase for each additional sUA category. The PBAC considered that this relationship is not robust or well established, and noted that none of the included trials demonstrated a benefit for flares, despite reduced sUA levels.
- Last observation carried forward (LOCF) was used to extrapolate sUA response from the FACT and APEX trials. The PBAC noted that the EXCEL trial (at 3 years) did not find any significant difference between febuxostat (both dosages) and allopurinol in sUA response or flares.

The PBAC noted that in addition to the above issues, the ESC highlighted the following concerns:

- FACT (52 week trial) and APEX (28 week trial) were used in the model but only APEX has a placebo arm, which is used in the model;
- The IMS cross-section retrospective observational cohort for utility values (EQ5D) was used despite no evidence of QoL gain in the trials.

Overall, the PBAC considered that the model presented in the submission was not a robust basis for making a subsidisation recommendation, and that the ICER was not reliable.

The PBAC noted the cost minimisation analysis of febuxostat (80mg and 120mg/d) versus allopurinol (300mg/d), conducted during the evaluation and corrected in the sponsor’s pre-sub-committee response (PSCR p4), resulted in a dispensed price for maximum quantity (DPMQ) that was less than one sixth of the requested price for the 80 mg strength. The PBAC noted the sponsor’s advice that it was not realistic that febuxostat could be launched in Australia at the cost-minimised price.

The PBAC noted the submission estimated an ICER less than \$15,000 per QALY when febuxostat 80mg was compared to placebo. The PBAC considered that febuxostat may potentially be a cost effective treatment of gout in patients unable to continue treatment with

allopurinol due to intolerance (i.e., a second-line setting, in which placebo would be an appropriate comparator). However, the economic model presented in the submission did not allow PBAC to be confident of the value of febuxostat in this particular population.

11. Estimated PBS Usage and Financial Implications

The PBAC noted that the utilisation estimates for the requested population appeared low. The estimated proportion of allopurinol and probenecid use related to gout was considered low and the overall estimates were highly sensitive to this assumption. The PBAC considered that there may also be a large untreated pool, including patients who have not persisted with treatment and patients who are treating their symptoms with over the counter NSAIDs.

A sensitivity analysis conducted by the Drug Utilisation Sub-Committee (DUSC) showed that the financial implications were most sensitive to the proportion of allopurinol and probenecid that were assumed to be for gout, and the assumed market uptake for febuxostat. A sensitivity analysis assuming adherence of 75% and assuming 90% of allopurinol and probenecid utilisation for gout resulted in a total cost in the range of 30-60 million in year five of listing.

The PBAC considered that both the epidemiological and the market share approaches underestimated the likely use (and therefore cost) for the first line restriction requested in the submission.

The PBAC considered the DUSC advice in relation to defining the potential febuxostat second-line population of patients who are unable to tolerate allopurinol:

- The incidence of allopurinol hypersensitivity is unknown; although it is estimated to be approximately 0.1%.² Allopurinol hypersensitivity can manifest in differing severity, with the most serious being severe cutaneous adverse reactions (i.e. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis), occurring in about one person in 56,000 per year.³
- Given that probenecid is less effective at reducing uric acid levels than allopurinol, it could be assumed that patients take probenecid when they are contraindicated to allopurinol and this could be a proxy for allopurinol intolerance. 1,214,530 allopurinol prescriptions and 19,061 probenecid prescriptions were supplied on the R/PBS in 2012-13; therefore probenecid prescriptions accounted for 1.5% of the total gout prescriptions (allopurinol plus probenecid).
- A review by Wortmann⁴ (2005) suggested approximately 5% of patients treated with allopurinol discontinued due to AEs. This paper may give an indication of the proportion of patients unable to continue to take allopurinol due to adverse effects (who could potentially use febuxostat second line).

The PBAC therefore considered that it was reasonable to estimate that between 0.1 and 5% of patients would be intolerant of allopurinol.

² Dalbeth, N. and Stamp, L. Allopurinol Dosing in Renal Impairment: Walking the Tightrope Between Adequate Urate Lowering and Adverse Events Seminars in Dialysis—Vol 20, No 5 (September–October) 2007 pp. 391–395.

³ <http://www.nps.org.au/health-professionals/health-news-evidence/2013/allopurinol-hypersensitivity>

⁴ Wortmann, R. "Recent advances in the management of gout and hyperuricemia." *Curr Opin Rheumatol*, 2005: 17:319–24.

12. PBAC Outcome

The PBAC did not recommend the listing of febuxostat. The PBAC considered the submission did not establish that febuxostat is superior in terms of comparative effectiveness over allopurinol. The PBAC considered that the trials presented in the submission overall did not demonstrate superior effectiveness to allopurinol for patient-relevant outcomes such as reduction in acute gout attacks or tophi, or improvement in QoL.

The PBAC considered that the advantage of a faster reduction in sUA did not translate into benefits over allopurinol for more clinically meaningful outcomes such as flare reduction, tophi resolution or health-related quality of life (HRQoL). Therefore, the PBAC did not support the submission's assumption that attaining the biological sUA target would lead to clinically meaningful outcomes.

The PBAC observed that with long term treatment, febuxostat appeared to lose its advantage over allopurinol in sUA reduction in the EXCEL trial and that there was a lack of evidence comparing febuxostat and with allopurinol at doses likely to be used in clinical practice (up to 900mg/day).

The PBAC considered the ICER was not informative for decision making for the first line treatment with febuxostat. The PBAC considered that the model was not valid as numerous assumptions were not supported by clinical evidence, and were highly favourable to febuxostat.

The PBAC recognised that there is a clinical need for an alternative treatment for patients, who are intolerant of allopurinol. The PBAC considered that an allopurinol-intolerant population consistent with the definition used in the NICE guidance for "*Febuxostat for the management of hyperuricaemia in people with gout*", may be an appropriate basis for defining a second-line treatment setting for febuxostat. However, the PBAC noted that the submission did not present clinical evidence to support the use of febuxostat in a second-line setting.

The PBAC considered that it may be possible to demonstrate acceptable cost-effectiveness of febuxostat versus placebo in the second-line treatment setting for patients intolerant of allopurinol. On the basis of the DUSC advice, the PBAC considered that it was reasonable to estimate that between 0.1 and 5% of patients would be intolerant of allopurinol.

The PBAC noted that this submission meets the criteria for an Independent Review.

Outcome:

Rejected

13. 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.

14. Sponsor's Comment

While the sponsor is disappointed with the decision, Menarini will work with PBAC to achieve a PBS listing for febuxostat in a cost-effective population and will work towards best defining such a second-line population.