

**7.01 FEBUXOSTAT,  
80 mg tablet, 28,  
Adenuric<sup>®</sup>, A.Menarini Australia Pty Ltd**

**1 Purpose of Application**

1.1 The major re-submission sought an Authority required (STREAMLINED) listing for the second-line treatment of chronic symptomatic gout.

**2 Requested listing**

2.1 The re-submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
FEBUXOSTAT Tablets 80 mg	28	5	\$ [REDACTED]	Adenuric A.Menarini

Treatment phase:	
Episodicity	Chronic
Severity	Symptomatic
Condition	Hyperuricaemia with deposition (chronic gout)
Restriction	Section 85 (General Schedule) Authority required (STREAMLINED) Initial and continuing
Treatment criteria	The patient must have received previous treatment with allopurinol for this condition
Clinical criteria	The patient must have a medical contraindication to allopurinol, a documented history of allopurinol hypersensitivity syndrome, or other intolerance to allopurinol warranting permanent discontinuation of treatment; OR The patient must have a serum uric acid measurement >357 µmol/L (6 mg/dL) despite a titrated allopurinol dose ≥600 mg/day, or have had such a measurement prior to initiation of treatment with febuxostat; OR The patient must have moderate to severe renal impairment, equivalent to Stage III or greater Chronic Kidney Disease (eGFR <60 ml/min/1.73 m <sup>2</sup> ), and have a serum uric acid measurement >357 µmol/L (6 mg/dL) despite the maximum titrated dose of allopurinol permitted by renal function status.

2.2 The treatment criterion of ‘The patient must have received previous treatment with allopurinol for this condition’ was incompatible with the clinical criterion that a ‘patient must have a medical contraindication to allopurinol’.

2.3 A clinical issue identified in the ESC advice was whether the requested restriction had adequately identified the population for whom febuxostat would benefit most. The ESC acknowledged the need for a second line drug in the treatment of gout, for patients with allopurinol-intolerance, or inadequate response to allopurinol (“allopurinol-insufficient”), but noted that no data were presented on the use of febuxostat in these specific patient populations.

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

### **3 Background**

- 3.1 Febuxostat was included on the Australian Register of Therapeutic Goods (ARTG) on 18 December 2014 and is 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.
- 3.2 This was the second submission to list febuxostat on the PBS.
- 3.3 In March 2014, the PBAC rejected a submission that sought to list febuxostat as a first-line therapy for gout.
- 3.4 The PBAC considered the March 2014 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 quality of life (QoL).
- 3.5 The PBAC considered that the advantage of a faster reduction in serum uric acid (sUA) may 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.
- 3.6 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.

### **4 Clinical place for the proposed therapy**

- 4.1 In the re-submission, febuxostat was proposed to be a second-line treatment, as an alternative to allopurinol in instances of allopurinol intolerance or when the effect of allopurinol is insufficient (defined as serum uric acid (sUA)  $\leq 357 \mu\text{mol/l}$ ).

### **5 Comparator**

- 5.1 The re-submission nominated the following comparators, depending on the treatment population:

Comparators

'Allopurinol inappropriate'	'Allopurinol insufficient'
<ul style="list-style-type: none"> <li>• Probenecid (≈2 g/day); or</li> <li>• Placebo (i.e. no urate lowering therapy)</li> </ul>	<ul style="list-style-type: none"> <li>• Probenecid (≈1 g/day) + allopurinol (≈300 mg/day); or</li> <li>• Probenecid (≈2 g/day); or</li> <li>• Allopurinol (optimally titrated dose); or</li> <li>• Placebo (i.e. no urate lowering therapy)</li> </ul>

5.2 The evaluation considered the nominated comparators to be appropriate for the respective patient populations. However the re-submission did not nominate the proportional mix of these comparators for each population. The ESC noted that based on Stamp et al. (2014), the doses of allopurinol being used in clinical practice may be sub-optimal.

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

## 6 Consideration of the evidence

### **Sponsor hearing**

6.1 The sponsor did not request a hearing for this item.

### **Consumer comments**

6.2 There were no consumer comments received for this item.

### **Clinical trials and studies**

6.3 The re-submission was based on the trials and studies summarised in the table below. The inclusion and exclusion of some studies by the re-submission were considered inappropriate for various reasons (e.g. allopurinol treatment naïve patients, no allopurinol dose titration beyond 300 mg/day). Thus, some studies included by the re-submission were not considered in the Commentary and other studies from the excluded list were included in the evidence during the evaluation. This included the CONFIRMS trial previously presented in the March 2014 submission, which was the only trial that had been previously considered by the PBAC.

Trials and studies included in the submission

Treatment	Requested PBS population		
	Allopurinol inappropriate	Allopurinol insufficient	"Allopurinol insufficient + RI" <sup>a</sup>
Febuxostat	Chohan 2011 – SA, n=13	-	TMX-67-203 - RCT v PBO, n=64 TMX-00-004 – RCT v PBO, n=115 FOCUS – extension to TMX-00-004 CONFIRMS – RCT v ALO, n=2269
Probenecid	Pui 2013 – comp. with PRO + ALO, n=30	Reinders 2009a – RCT v BENZ, n=31	Pui 2013 provides some data in those with eGFR <50 ml/min/1.73 m <sup>2</sup> (n=9)
Allopurinol up-titration	-	Jennings 2014 – SA, n=400 Stamp 2011 – comp. NDE, n=90 Baumgartner 2013 – SA, n=1732 Perez-Ruiz 1998 – comp. with BENZ, n=49 Reinders 2009b – RCT v BENZ, n=17	-
Probenecid + allopurinol	-	Pui 2013 – comp. with PRO, n=27 Reinders 2007 – SA, n=14 Stocker 2011 – SA, n=20	Pui 2013 provides some data in those with eGFR <50 ml/min/1.73 m <sup>2</sup> (n=6)

Abbreviations: SA=single arm, RCT=randomised controlled trial, PBO=placebo, ALO=allopurinol RI=renal impairment, sUA=serum uric acid, QD=once daily, BID=twice daily, comp.=comparison (not randomised), NDE=non-dose escalation  
<sup>a</sup> while the requested population is those in whom allopurinol has been insufficient who have renal impairment (RI), the studies only inform the efficacy and safety of therapies in those with renal impairment

6.4 The evidence to support the application in the re-submission was not strong for the following reasons:

- No evidence was presented to show the efficacy and safety of febuxostat in those in whom allopurinol is insufficient (with or without renal impairment). While the TMX-67-203, TMX-00-004, and CONFIRMS trials and the FOCUS extension study included patients with renal impairment, patients in these trials/studies were not required to have had insufficient effect with maximally tolerated doses of allopurinol.
- Although Chohan (2011) presented data relating to the efficacy and safety of febuxostat in patients with documented adverse events to allopurinol, this study was relatively small and provided no comparative data.
- Similarly, the evidence presented for the relevant comparators was deficient. Although some randomised-controlled studies and comparative studies were included, with the exception of Pui (2013), only a single-arm of the trials/studies were relevant to the submission.
- The data did not permit indirect comparisons across the treatments under consideration.

6.5 Citations for the studies presented in the re-submission are provided in the table below.

Public Summary Document – March 2015 PBAC Meeting

Citations for the studies presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Allopurinol inappropriate</b>		
Chohan 2011 [FBX single arm]	Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions.	<i>J Rheumatol</i> , 2011: 38(9):1957-9.
Pui 2013 – includes a [PRO arm, includes a PRO + ALO arm for ALO insufficient]	Pui K, et al. Efficacy and tolerability of probenecid as urate-lowering therapy in gout; clinical experience in high-prevalence population.	<i>J Rheumatol</i> , 2013: 40(6):872-6.
<b>Alluopurinol insufficient (no renal impairment)</b>		
<b>Treated to target of sUA <math>\leq</math>357<math>\mu</math>mol/L (6mg/dL)</b>		
Jennings	Jennings C, et al. Up-titration of allopurinol in subjects with gout.	<i>Semin Arthritis Rheum</i> , 2014: 44(1):25-30.
Stamp	Stamp L, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in subjects with chronic gout, including those with renal impairment.	<i>Arthritis Rheum</i> , 2011: 63(2):412-21.
Baumgartner	Allopurinol dose titration and efficacy: A large-scale, 6-month, multicenter, prospective study.	<i>Arthritis and Rheumatism</i> , 2013: 65 SUPPL. 10 (S503-S504).
Perez-Ruiz	Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout.	<i>Ann Rheum Dis</i> , 1998: 57(9):545-9
Pui	Efficacy and tolerability of probenecid as urate-lowering therapy in gout; clinical experience in high-prevalence population.	<i>J Rheumatol</i> , 2013: 40(6):872-6.
<b>ALO dose not treated to sUA target specified in the restriction</b>		
Reinders 2009b [ALO single arm]	A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in subjects with gout.	<i>Ann Rheum Dis</i> , 2009: 68(6):892-7.
Reinders 2009a [PRO single arm]	Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol.	<i>Ann Rheum Dis</i> , 2009: 68(1):51-6.
Reinders [PRO + ALO single arm]	Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout subjects.	<i>Clin Rheumatol</i> , 2007: 26(9):1459-6.
Stocker [PRO + ALO single arm]	Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in subjects with gout.	<i>J Rheumatol</i> , 2011: 38(5):904-10.
<b>Allopurinol insufficient + renal impairment<sup>a</sup></b>		
TMX-67-203 [RCT of FBX v PBO]	A Multicenter, Randomized, Double-Blind, Phase 2 Study to Evaluate the Effect of Febuxostat versus Placebo on Renal Function in Gout Subjects with Hyperuricemia and Moderate to Severe Renal Impairment  Saag K, et al. Effect of febuxostat on serum urate levels in gout subjects with hyperuricemia and moderate-to-severe renal impairment: A randomized controlled trial."	26 April 2013  <i>Arthritis &amp; Rheumatism</i> , 2013: 65 Suppl. 10:S498-499.
TMX-00-004 [RCT of FBX v PBO; sub-group of patients with RI]	Phase II, dose-response, safety and efficacy study of oral febuxostat (TMX-67) in subjects with gout.  Becker MA, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: A twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in subjects with gout.	2 September 2005  <i>Arthritis &amp; Rheumatism</i> , 2005: 52(3), 916-923.

Public Summary Document – March 2015 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
FOCUS [FBX single arm; extension of TMX- 00-004]	Phase 2, open-label study to assess the long-term safety of oral febuxostat in subjects with gout.	11 March 2008
	Schumacher HR, et al. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study.	<i>Rheumatology (Oxford)</i> , 2009; 48(2), 188-194.
<i>CONFIRMS</i> [RCT of FBX v ALO; sub-group of patients with RI]	<i>A Phase 3, Randomized, Multicenter, Double-Blind, Allopurinol-Controlled Study Assessing the Safety and Efficacy of Oral Febuxostat in Patients with Gout</i>	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."	<i>Arthritis Res Ther</i> , 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."	<i>Nucleosides Nucleotides Nucleic Acids</i> , 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."	<i>BMC Geriatr</i> , 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."	<i>BMC Musculoskelet Disord.</i> , 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."	<i>Clin Ther</i> , 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."	<i>Arthritis Care Res (Hoboken)</i> , 2012: Feb;64(2):256-61.

*Trials and studies in italics were included during the evaluation*

- 6.6 The ESC noted that a systematic review and meta-analysis by Castrejon et al. (2014)<sup>1</sup> of allopurinol's safety compared with other urate lowering drugs became available in December 2014 during the period of the evaluation and so was not presented in the re-submission or evaluated in the Commentary. This study contained relevant data regarding the comparative safety of febuxostat.
- 6.7 The key features of the studies assessed in the re-submission are provided in the table below.

<sup>1</sup> Castrejon, I et al, Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis. *Rheumatol Int.* 2014 Dec 18. [Epub ahead of print]

Key features of the included evidence

Trial	N <sup>b</sup>	Design/ duration	Treatment	Risk of bias	Patient population	Outcome - sUA	Use in modelled evaluation
<b>Allopurinol inappropriate</b>							
Chohan 2011	13	Re, SA, 15 mths	FBX	High	Allopurinol intolerance	<357µmol	Yes
Pui 2013	30	Re, OBS, 3 mths	PRO	High			No
<b>Allopurinol insufficient</b>							
Reinders 2009a <sup>a</sup>	31	RCT, OL, 2 mths	PRO	High	Insufficient effect with allopurinol	<297µmol	No
Jennings 2014	144	Pros, SA, [NR]	ALO-up	High		<357µmol	No
<i>Stamp 2011</i>	45	<i>NR, OL, 12 mths</i>	<i>ALO-up</i>	<i>High</i>		<357µmol	No
<i>Baumgartner 2013</i>	1732	<i>SA, OL, 6 mths</i>	<i>ALO-up</i>	<i>High</i>		<357µmol	No
<i>Perez-Ruiz 1998</i>	23	<i>Pros, NR, 12 mths</i>	<i>ALO-up</i>	<i>High</i>		<357µmol	No
Reinders 2009b <sup>a</sup>	17	RCT, OL, >2 mths	ALO-up	High		<297µmol	Yes
Pui 2013	27	Re, OBS, 3 mths	ALO+PRO	High		<357µmol	Yes
Reinders 2007 <sup>a</sup>	14	RCT, OL, >2 mths	ALO+PRO	High		<297µmol	No
Stocker 2011	19	OL, OBS, [NR]	ALO+PRO	High		<357µmol	No
<b>Allopurinol</b>							
TMX-67-203	63	R, DB, [NR]	FBX, PBO	Low	Renal impairment (not + insufficient ALO)	<357µmol	Yes
TMX-00-007	106	R, DB, 1 mth	FBX, PBO	Low		<357µmol	No
FOCUS	68	OL Ext	FBX	High		<357µmol	Yes
<i>CONFIRMS</i>	402 <sup>b</sup>	<i>R, DB, 6 mths</i>	<i>FBX, ALO</i>	<i>Low</i>		<357µmol	No

FBX=febuxostat, ALO-up=allopurinol up-titration, PRO=probenecid, ALO+PRO=allopurinol + probenecid, PBO=placebo, Re=retrospective, OBS=observational, RCT=randomised controlled trial, OL=open-label, Pros=prospective, NR=non-randomised, [NR]=not reported, R=randomised, DB=double blind; OL Ext=open-label extension

<sup>a</sup> only one arm relevant

<sup>b</sup> moderate renal impairment sub-group (defined as eGFR ≤60 ml/ml/1.73 m<sup>2</sup>)

*Trials and studies in italics were included during the evaluation*

- 6.8 Only the TMX-67-203, TMX-00-004 and CONFIRMS trials were considered to be of low risk of bias by the evaluation. All other studies and trials were considered to be high risk as they were open-label or were retrospective in design or single-arm.

**Comparative effectiveness**

- 6.9 The table below summarises the proportion of patients achieving target sUA levels.

Proportion of patients achieving target sUA levels

	ALO inappropriate	ALO insufficient		Renal Impairment (RI)
Target sUA, n/N (%)	<357 µmol/l	<297 µmol/l	<357 µmol/l	<357 µmol/l
Chohan 2011 (FBX)	10/13 (77)	-	-	-
Pui 2013 (PRO)	10/30 (33)	-	-	-
Reinders 2009a (PRO)	-	20/31 (65)	NA	-
Jennings 2014 (ALO-up)	-	NA	139/144 (97)	-
Stamp 2011 (ALO-up)	-	NA	31/45 (69)	-
Baumgartner 2013 (ALO-up)	-	NA	745/1732 (43)	-
Perez-Ruiz 1998 (ALO-up)	-	NA	23/23 (100)	-
Reinders 2009b (ALO-up)	-	NR	NA	-
Pui 2013 (ALO+PRO)	-	NA	10/27 (37)	-
Reinders 2007 (ALO+PRO)	-	12/14 (86)	14/14 (100)	-
Stocker 2011 (ALO+PRO)	-	NR	NA	-
TMX-67-203 – 12 months All patients had level of RI	-	-	-	F40/80:14/31 (45); PBO: 0/32 (0)
TMX-00-004 – 1 month RI sub-group	-	-	-	FBX40: 9/18 (50) FBX80: 15/19 (79) PBO: 0/19 (0)
FOCUS – 60 months RI sub-group	-	-	-	FBX40: 3/3 (100) FBX80: 23/24 (96)
CONFIRMS – 6 months RI sub-group	-	-	-	FBX40: 56/130 (43) FBX80: 97/136 (71) ALO200: 43/136 (32)

NA=not applicable as it was not a measured outcome, NR=not reported

- 6.10 Data from Chohan 2011 and Pui 2013 indicated that patients with allopurinol intolerance responded to treatment with febuxostat or probenecid in terms of sUA lowering. Although no comparison between these studies was possible, the response rate to febuxostat appeared to be higher. This may have been due to the dose of febuxostat being optimised for individual patients and the possibility that probenecid was being used at sub-therapeutic doses (1.29 g, with 2 g being the maximum dose).
- 6.11 Allopurinol up-titration, or the addition of/switching to probenecid amongst those who were allopurinol insufficient led to 37-100% of patients achieving sUA levels <357 µmol/l.
- 6.12 A statistically significantly greater proportion of patients treated with febuxostat 40 mg and 80 mg achieved target sUA doses in the TMX-67-203 and TMX-00-004 trials compared with those treated with placebo (in both the ITT group and in the renal impairment sub-group). A statistically significantly greater proportion of patients treated with febuxostat 80 mg achieved target sUA doses in CONFIRMS. No differences were observed when comparing febuxostat 40 mg/day with allopurinol (300 mg/day in the absence of renal-impairment and 200 mg/day in renal-impairment patients).

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

### Harms

- 6.13 The table below summarises the proportion of patients discontinuing treatment due to an adverse event.

Proportion of patients discontinuing treatment due to an adverse event

	ALO inappropriate	ALO insufficient	Renal Impairment (RI)
Chohan 2011 (FBX)	1/13 (8)	-	-
Pui 2013 (PRO & ALO+PRO)	7/57 (12)		-
Reinders 2009a (PRO)	-	8/31 (26)	-
Jennings 2014 (ALO-up)	-	0/144 (0)	-
Stamp 2011 (ALO-up)	-	3/45 (7)	-
Baumgartner 2013 (ALO-up)	-	NR	-
Perez-Ruiz 1998 (ALO-up)	-	NR	-
Reinders 2009b (ALO-up)	-	0/17 (0)	-
Reinders 2007 (ALO+PRO)	-	0/14 (0)	-
Stocker 2011 (ALO+PRO)	-	0/20 (0)	-
TMX-67-203 – 12 months	-	-	FBX40/80: 3/32 (9.4) PBO: 9/32 (28)
TMX-00-004 – 1 month	-	-	FBX40: 1/37 (3) FBX80: 2/40 (5) PBO: 1/38 (3)
FOCUS – 60 months	-	-	FBX40: 1/8 (13) FBX80: 10/79 (13)
CONFIRMS – 6 months	-	-	FBX40: 49/757 (7) FBX80: 61/756 (8) ALO: 64/756 (9)

- 6.14 In its consideration of the previous submission, the PBAC noted that 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 (80 mg or 120 mg) 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 more patients treated with febuxostat 120 mg who discontinued treatment due to flares and adverse events compared to allopurinol (RR (95%CI): 3.42 (1.72, 6.81)). More patients treated with febuxostat 80 mg experienced hypertension compared to allopurinol (RR (95%CI) 4.35 (1.25, 15.09). However, this was only seen 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 80 mg, 120 mg and allopurinol respectively.
- 6.15 Data from the trials and studies included in the re-submission to the March 2015 PBAC meeting did not indicate any new safety signals.
- 6.16 The ESC noted that the finding of Castrejon et al. (2014) that the incidence of adverse events was similar between allopurinol (range 38.6-85) and febuxostat (range 41.8-80) treated patients. Six patients on febuxostat and three on allopurinol died during the studies; no deaths were judged related to drug therapy. The combined risk of adverse events was RR = 1.04 (95 % CI 0.98, 1.11). Castrejon et al. (2014) concluded that allopurinol is a safe option that may be slightly favourable compared to other urate lowering drugs.

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

**Benefits/harms**

- 6.17 A benefits/harms table was not compiled as the re-submission did not present data to allow an assessment of the efficacy and safety of febuxostat compared to the alternative treatments for any of the populations for whom listing was sought.

**Clinical claim**

- 6.18 The re-submission appropriately did not make a formal clinical claim regarding the comparative efficacy and safety of febuxostat versus the relevant comparators for any of the populations for whom listing was sought. The re-submission asserted that  $\leq 25\%$  of subjects on allopurinol either cannot tolerate dose titration or cannot achieve sUA  $\leq 357 \mu\text{mol/L}$  with maximal doses. The submission claimed that febuxostat is an alternative to probenecid monotherapy or combination therapy (probenecid added to allopurinol) in these patients and that its efficacy and safety had been demonstrated in a range of relevant populations and is maintained for up to five years. No data were presented on the use of febuxostat in allopurinol insufficient patients. The febuxostat study in patients with renal impairment and the 5-year febuxostat study had a 50% (approximately) dropout rate.

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

**Economic analysis**

- 6.19 The economic analysis presented was a cost-per-responder analysis (response defined as achievement of serum uric acid levels  $< 357 \mu\text{mol/l}$ ) of febuxostat compared with placebo and each of the three nominated comparators versus placebo.
- 6.20 The economic analysis was a simple decision tree analysis that considered drug treatment costs and the proportion of patients who reached sUA  $< 357 \mu\text{mol/L}$  (responders). The table below summarises the model structure.

Summary of model structure and rationale

Time horizon	One year. (Studies presented in the submission ranged from 2 months to 5 years)
Outcomes	If sUA $\leq 357 \mu\text{mol/L}$ at the end of one year the subject was classified as a responder.
Methods used to generate results	Simple decision tree
Cycle length	One year
Transition probabilities	Response rates and Discontinuation rates (see the table below)
Discount rate	Not applicable
Software package	TreeAge Pro 2014

- 6.21 The table below summarises the variables in the economic analysis.

Public Summary Document – March 2015 PBAC Meeting

Variables in the economic evaluation

Treatment strategies	Mean dose	Cost/year	Discont. rate	TTD (years)	Response probability	
					All patients	Continuers <sup>a</sup>
<b>Allopurinol inappropriate patients</b>						
Febuxostat	55 mg/day	\$ [REDACTED]	7.7%	0.077	76.9%	83.3%
Probenecid	2 g/day	\$1,110.04	25.8%	0.154	67.7%	91.3%
Placebo	no ULT	\$0	0.0%	NA	0.0%	0
<b>Allopurinol insufficient patients</b>						
Febuxostat	76 mg/day	\$ [REDACTED]	32.8%	0.445 <sup>d</sup>	85.5% <sup>b</sup>	>100%
Probenecid + allopurinol	1 g/day + 243mg/day	\$605.18	0.0%	NA	100.0%	100%
Probenecid	2g/day	\$1,110.04	25.8%	0.154	67.7%	91.3%
Allopurinol	600mg/day	\$123.84	0.0%	NA	0.0%	0%
Placebo	no ULT	\$0	0.0%	NA	0.0%	0%
<b>Allopurinol insufficient patients with moderate to severe renal impairment</b>						
Febuxostat	65 mg/day	\$ [REDACTED]	28.1%	0.462 <sup>d</sup>	45.2%	62.9% <sup>c</sup>
Probenecid + allopurinol	0.99 g/day + 362mg/day	\$624.19	25.0% <sup>e</sup>	0.462 <sup>d</sup>	50.0% <sup>b</sup>	66.7%
Probenecid	1.29 g/day	\$715.97	25.0% <sup>e</sup>	0.462 <sup>d</sup>	22.0% <sup>b</sup>	29.3%
Allopurinol	200 mg/day	\$41.28	0.0%	NA	0.0%	0%
Placebo	no ULT	\$0	0.0%	NA	0.0%	0%

Source: Constructed during the evaluation from Table D-1 of the re-submission

TTD = time to treatment discontinuation.

<sup>a</sup> calculated as response rate/(1-discontinuation rate)

<sup>b</sup> rate applied in the analysis presented in the re-submission

<sup>c</sup> incorrectly estimated at 58.3% in the re-submission

<sup>d</sup> It is unclear how the TTD was estimated.

<sup>e</sup> The re-submission states that this discontinuation rate was estimated. The discontinuation rate for probenecid monotherapy and combination therapy combined is 12.3%.

6.22 The tables below summarise the results of the economic analysis.

Results of the economic evaluation: Allopurinol inappropriate patients

	Cost	Response probability	Cost/responder
Placebo (PBO)	0	0	N/A
Probenecid (PRO)	\$867.75	0.6774	\$1,280
Febuxostat (FBX)	\$ [REDACTED]	0.7689	\$ [REDACTED]
<b>Incremental analysis</b>			
Comparison	Incremental cost	Incremental response probability	ICER
FBX versus PBO	\$ [REDACTED]	0.7689	\$ [REDACTED]
FBX versus PRO <sup>a</sup>	-\$ [REDACTED]	0.0915	Dominant

Source: Table D-2 of re-submission and TreeAgePro results.

<sup>a</sup> PRO versus FBX results presented as FBX versus PRO in the re-submission

Results of the economic evaluation: Allopurinol insufficient patients

	Cost	Response probability	Cost/responder
Placebo (PBO)	0	0	N/A
Allopurinol (ALO)	\$123.84	0	N/A
Probenecid (PRO)	\$867.75	0.6774	\$1,281
Febuxostat (FBX)	\$ [REDACTED]	0.855 <sup>a</sup>	\$608
ALO + PRO	\$605.18	1.0	\$605
Incremental analysis			
Comparison	Incremental cost	Incremental response probability	ICER
FBX versus PBO	\$ [REDACTED]	0.855	\$ [REDACTED]
FBX versus ALO	\$ [REDACTED]	0.855	\$ [REDACTED]
FBX versus PRO	-\$ [REDACTED]	0.1776	Dominant
FBX versus ALO + PRO	-\$ [REDACTED]	-0.145	FBX less costly & effective

Source: Table D-3 of re-submission and TreeAgePro results.

<sup>a</sup> Table D-3, p89 indicates that the response rate to febuxostat is 0.5746 – derived from  $(1-0.328)*0.855$  (responder rate applied to continuing patients).

Abbreviations: ALO=allopurinol; FBX= febuxostat; PBO = placebo; PRO = probenecid

Results of the economic evaluation: Allopurinol insufficient + Renal Impairment patients

	Cost	Response probability	Cost/responder
Placebo (PBO)	0	0	N/A
Allopurinol (ALO)	\$41.28	0	N/A
Probenecid (PRO)	\$619.68	0.22 <sup>a</sup>	\$2,817
Febuxostat (FBX)	\$ [REDACTED]	0.452 <sup>b</sup>	\$ [REDACTED]
ALO + PRO	\$540.23	0.50 <sup>c</sup>	\$1,080
Incremental analysis			
Comparison	Incremental cost	Incremental response probability	ICER
FBX versus PBO	\$ [REDACTED]	0.452	\$ [REDACTED]
FBX versus ALO	\$ [REDACTED]	0.452	\$ [REDACTED]
FBX versus PRO	-\$ [REDACTED]	0.232	Dominant
FBX versus ALO+PRO	-\$ [REDACTED]	-0.048	FBX less costly & effective

Source: Table D-4 of re-submission and TreeAgePro results.

Table D-4, p90 of the submission cites the following response rates (derived from  $((1-\text{discontinuation rate}) * \text{response rate})$ )

<sup>a</sup> 0.165, <sup>b</sup> 0.4921 (response rate cited as 58.3%, should be 53.6%, <sup>c</sup> 0.375

Abbreviations: ALO=allopurinol; FBX= febuxostat; PBO = placebo; PRO = probenecid

- 6.23 The variation in febuxostat’s cost-effectiveness profile across these three patient populations highlighted concern about the applicability of the data sources. The response rate data came from small studies in disparate populations. None of the data sources compared febuxostat directly with any of the comparators.
- 6.24 The evaluation questioned whether the cost per responder analysis presented in the re-submission was informative, given that it provided a limited basis to assess the value of the health benefit of response. Further, the evaluation identified that meaningful interpretation of the results of the economic analysis was confounded by the fact that a responder was defined based on a sUA threshold achievement, when sUA had not been accepted to be a reliable surrogate outcome for clinical events in the population of interest.

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

Drug cost/patient/year: \$ [REDACTED]

6.25 Based on 13 packs per patient per year, a dose of 80 mg/day and the proposed DPMQ of \$ [REDACTED].

**Estimated PBS usage & financial implications**

6.26 This re-submission was not considered by DUSC. DUSC advice to the PBAC had previously been provided on the initial submission considered in March 2014. The previous DUSC advice had been in the context of listing allopurinol in the first-line setting but also included additional advice about potential utilisation in a second-line setting.

6.27 The table below summarises febuxostat usage and cost estimates that were provided in the sponsor’s pre-sub-committee response and repeated in the pre-PBAC response following the sponsor’s adjustment for a potential simplified PBS-restriction definition of ‘allopurinol insufficient’ patients.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated use of Febuxostat and cost to PBS/RPBS</b>					
Untreated chronic gout patients (contraindicated or intolerant to allopurinol)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Allopurinol treated patients with inadequate control	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Probenecid treated patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Combination (allopurinol + probenecid) treated patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total potential patients who may be treated with febuxostat	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated net cost to the PBS/RPBS</b>					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Section E Workbook.xls, sponsor pre-sub-committee response, E2 worksheet, rows 4 to 8 and row 38

- 6.28 The redacted table shows that the estimated number of patients who may be treated with febuxostat is 10,000-50,000 in Year 1 and 2, and 50,000-100,000 in Years 3-5. The estimated net cost to the PBS is less than \$10 million in Year 1, between \$10 million and \$20 million in Year 2 and >\$20 million in Year 5.
- 6.29 The listing of febuxostat was projected to result in a net cost to the RPBS/PBS, due to febuxostat predominantly replacing use of allopurinol which is lower in cost. Ultimately, the evaluation advised that the estimates were only reasonable if it is considered that (i) the requested restriction for febuxostat would change the treatment algorithm such that patients with gout would undertake allopurinol dose titration and (ii) the requested listing for febuxostat would sufficiently restrict use to patients in whom allopurinol dose titration has been trialled and failed, and in those who are allopurinol intolerant.
- 6.30 The estimates also assumed that allopurinol titration is the current management approach, rather than assuming that the listing of febuxostat and changes to the treatment algorithm for gout would occur simultaneously. In assuming that allopurinol is the current management for patients with gout, this allows for allopurinol insufficient patients to be treated with febuxostat for the whole year in Year 1 (which substitutes for a year of continued use of titrated allopurinol, despite not achieving target sUA levels). In a scenario where the listing of febuxostat and changes to the treatment algorithm occur simultaneously, patients who are allopurinol insufficient could not be treated with febuxostat in Year 1 as titration with allopurinol is assumed to occur over a period of one year. The sponsor's pre-sub-committee response corrected for this assumption.
- 6.31 The evaluation questioned whether the submission's estimates of use and financial implications were accurate. The ESC noted that the re-submission proposed a risk sharing agreement consisting of a cap on patient numbers, and a rebate, to achieve greater certainty in expected changes in Commonwealth financial expenditure. The ESC advised that there is little robust epidemiological data on allopurinol intolerance or allopurinol insufficient gout available to inform what an appropriate cap would be. The ESC considered that the best proxy estimate for the number of such patients is the proportion of prescriptions for probenecid (which makes up <2% of prescriptions for gout patients) as opposed to 10% as claimed in submission. The ESC further considered that an insufficient response to allopurinol is in most cases due to poor adherence and under-dosing. Dose escalation is effective in the large majority of gout patients (e.g. 89%, in Stamp et al. 2014, suggesting a maximum of 11% may be allopurinol insufficient)<sup>2</sup>.

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

### **Quality Use of Medicines**

- 6.32 The sponsor suggested that a febuxostat listing would create an incentive for physicians to treat-to-target. Further, it was claimed that to gain acceptance and

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<sup>2</sup> Stamp, LK et al: Impaired response or insufficient dosage? – examining the potential causes of "inadequate response" to allopurinol in the treatment of gout. *Semin Arthritis Rheum.* 2014; 44(2):170-174

adherence, the restriction criteria would need to be supported by a body such as the National Prescribing Service.

***Financial Management – Risk Sharing Arrangements***

- 6.33 The sponsor signalled its willingness to enter into a risk sharing agreement based on a patient cap and rebate.

**7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of febuxostat as an Authority Required benefit. The listing recommended was for patients with a contraindication to, or intolerant of, treatment with allopurinol, on the basis of a clinical need for an alternative to probenecid in this patient population and on the basis that at the price proposed in the submission, febuxostat is likely to represent a cost-effective treatment compared to probenecid in a targeted, second line-treatment patient population. The PBAC did not recommend the listing of febuxostat for the patient population described by the submission as ‘allopurinol insufficient’ patients on the basis that inadequate clinical evidence had been presented to establish the cost-effectiveness of febuxostat in this setting.
- 7.2 The PBAC noted that the re-submission’s clinical placement of febuxostat as an alternative second-line treatment differed to the first line treatment setting proposed in the initial submission to the March 2014 PBAC meeting. The PBAC considered the proposed use of febuxostat as an alternative second-line treatment to be reasonable but was unsure whether in practice, febuxostat use would be limited to the second-line setting. The PBAC considered it possible that some febuxostat use would occur in the first-line setting. Therefore, the actual alternative (comparator) therapy most replaced by febuxostat in practice, could vary from the nominated comparators.

- 7.3 The resubmission's nominated comparators of probenecid ( $\approx 2$  g/day) or placebo (i.e. no urate lowering therapy) in allopurinol intolerant patients and probenecid ( $\approx 1$  g/day) + allopurinol ( $\approx 300$  mg/day) or probenecid ( $\approx 2$  g/day), or allopurinol (optimally titrated dose) or placebo in allopurinol insufficient patients reflected the submission's proposed clinical management algorithm. The PBAC's view was that optimal titration of allopurinol may not be occurring in clinical practice. Further, if allopurinol was consistently optimally titrated in patients with chronic gout, the PBAC's opinion was that there would be very few patients with inadequate response. Probenecid or placebo in allopurinol intolerant patients appeared to be the most relevant comparators.
- 7.4 The PBAC's main concern about the clinical evidence presented in the submission was the paucity of evidence of efficacy and safety of febuxostat in allopurinol insufficient patients (with or without renal impairment). While the TMX-67-203, TMX-00-004, and CONFIRMS trials and the FOCUS extension studies included patients with renal impairment, patients in these trials/studies were not required to have had insufficient effect with maximally tolerated doses of allopurinol. Therefore, the submission's request to list febuxostat in allopurinol insufficient patients was not adequately supported by the evidence available to the Committee.
- 7.5 The PBAC noted that the trial data suggested that febuxostat is an effective drug. A statistically significantly greater proportion of patients treated with febuxostat 40 mg and 80 mg achieved target sUA doses in the TMX-67-203 and TMX-00-004 trials compared with those treated with placebo (in both the ITT group and in the renal impairment sub-group). A statistically significantly greater proportion of patients treated with febuxostat 80 mg achieved target sUA doses in CONFIRMS. No differences were observed when comparing febuxostat 40 mg/day with allopurinol (300 mg/day in the absence of renal-impairment and 200 mg/day in renal-impairment patients). The PBAC further observed that data from Chohan 2011 and Pui 2013 indicated that patients with allopurinol intolerance responded to treatment with febuxostat or probenecid in terms of sUA lowering. Although the evaluation advised that no comparisons between these studies was possible, the response rate to febuxostat appeared to be higher. This may have been due to the dose of febuxostat being optimised for individual patients and the possibility that probenecid was being used at sub-therapeutic doses (1.29 g, with 2 g being the maximum dose).
- 7.6 The PBAC recalled that in its consideration of the previous submission (March 2014), a pooled safety analysis of trials with up to one year follow-up found that fewer total adverse events were reported by patients treated with febuxostat (80 mg or 120 mg) compared to patients treated with allopurinol (pooled RR (95%CI): 0.94 (0.89, 0.99) and 0.90 (0.84, 0.96) respectively). Data from the trials and studies included in the submission to the March 2015 PBAC meeting did not indicate any new safety signals. The PBAC therefore considered that the comparative harms of febuxostat were probably no worse than allopurinol, probenecid and allopurinol + probenecid.

- 7.7 The PBAC noted that its Minutes from its March 2014 meeting recorded that that it may be possible to demonstrate acceptable cost-effectiveness of febuxostat compared to placebo in the second-line treatment setting for patients intolerant of allopurinol. However, the March 2015 resubmission had presented a cost-per-responder analysis which compared febuxostat with placebo, probenecid, allopurinol and probenecid + allopurinol. For the reasons identified in the evaluation (see para 6.23 and 6.24), the PBAC's view was that the conclusions that could be drawn from the cost-per-responder analysis were limited.
- 7.8 The PBAC further noted that the evaluation and ESC provided a sensitivity analysis of estimated DPMQ for a febuxostat pack assuming various proportions of allopurinol inappropriate to insufficient patients, and varying assumed equi-effective doses of febuxostat compared with probenecid and allopurinol. This analysis was for consideration in the event that a cost-minimisation analysis was considered appropriate. However, non-inferior efficacy and safety between febuxostat and the comparators in the allopurinol insufficient patient population had not been established due to the absence of appropriate comparative data. Hence, construction of a febuxostat price from a cost-minimisation basis was not considered applicable in the circumstances. Instead, the PBAC considered that febuxostat at the proposed price in the submission was no more costly compared to probenecid in a patient population which is genuinely intolerant of, or contraindicated to allopurinol treatment.
- 7.9 The PBAC considered the resubmission estimates of use for patients intolerant to allopurinol likely to be overestimated. Based on the DUSC advice from the March 2014 meeting, between 0.1% and 5% of patients might be intolerant of allopurinol. This range was based on an estimated incidence of allopurinol hypersensitivity of 0.1% (Dalbeth & Stamp 2007) and the proportion of patients unable to continue to take allopurinol due to adverse effects estimated as 5% (Wortmann 2005). Similarly, the small size of the current probenecid market is another measure of the population likely to use febuxostat. The PBAC was of the view that an estimate of 5% of patients are unable to continue with allopurinol treatment due to adverse effects is conservative (i.e. the true number is likely to be less).
- 7.10 The PBAC also noted that an alternative approach to estimating use and financial implications were provided by the sponsor in the pre-sub-committee response and again in the pre-PBAC response, with revisions to account for the simplified restriction suggested by the Secretariat. The PBAC considered that the resubmission's financial estimates and revised estimates were high because they attempted to account for allopurinol insufficient patients under less stringent PBS restrictions than originally proposed by the submission. If the PBS population was limited to those intolerant of allopurinol or contraindicated to allopurinol, the PBAC expected that the financial implications would be less than those estimated by the submission.

- 7.11 To address concerns about use of febuxostat in the first line setting, the PBAC recommended an Authority Required listing and not an Authority Required (Streamlined). To reduce the risk of unexpected Commonwealth expenditure on febuxostat if used beyond the recommended listing, the PBAC recommended that a risk share agreement be implemented whereby financial expenditure beyond an agreed level would be rebated to the Commonwealth [REDACTED]. The PBAC advised that it would be reasonable for a risk share agreement expenditure cap to be calculated based on the conservative estimate that up to █% of patients with chronic gout cannot take allopurinol for reasons relating to contraindications or adverse effects. The PBAC further recommended that DUSC review febuxostat usage shortly after listing (i.e. after a period of 2 years) to ensure that usage is in line with estimates.
- 7.12 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, febuxostat should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.13 The PBAC advised that febuxostat is suitable for prescribing by nurse practitioners within a shared care model.
- 7.14 The PBAC recommended that the Safety Net 20 Day Rule should apply.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review.

**Outcome:**  
Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty. (units)	Max. Qty. (packs)	No. of Rpts	Proprietary Name and Manufacturer	
FEBUXOSTAT Febuxostat 80 mg tablet, 28	28	1	5	Adenuric	FK

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Chronic
Severity:	---
Condition:	gout
PBS Indication:	Chronic gout

Treatment phase:	----
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>The patient must have a medical contraindication to allopurinol; OR            The patient must have a documented history of allopurinol hypersensitivity syndrome; OR            The patient must have an intolerance to allopurinol necessitating permanent treatment discontinuation</p> <p>AND</p> <p>The condition must be either chronic gouty arthritis or chronic tophaceous gout</p>
Administrative advice	<p><u>Shared Care Model:</u>            For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

## 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

Menarini acknowledges that the PBAC has agreed to fund febuxostat in this high need group of chronic gout patients and continues to believe there is also an important unmet clinical need for febuxostat as an alternative therapy for patients who have had an insufficient response to their maximally tolerated dose of allopurinol.