PUBLIC SUMMARY DOCUMENT
Product: Milnacipran, capsules, 25 mg, 50 mg and 100 mg, Joncia®
Sponsor: Pierre Fabre Médicament Australia Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application
The submission requested a Restricted Benefit listing for the management of an adult patient with fibromyalgia, after failure of standard treatment options, who meets certain criteria.

2. Background
This was the first time the PBAC had considered the listing of milnacipran for fibromyalgia.

3. Registration Status
Milnacipran TGA registered on 17 November 2011 for the management of fibromyalgia.

4. Listing Requested and PBAC's View
Restricted benefit
Management of an adult patient with fibromyalgia, after failure of standard treatment options. Initiation of milnacipran is by a specialist qualified to diagnose fibromyalgia according to the 1990 American College of Rheumatology diagnosis criteria.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Fibromyalgia is a chronic pain syndrome characterised by widespread pain and is accompanied by fatigue, stiffness and sleep disturbances. The pain is due to modifications in biochemical functions within the pain system rather than a structural musculoskeletal defect. The main symptoms are muscle pain, fatigue, morning stiffness and sleep disturbances.

Fibromyalgia was defined by the American College of Rheumatology in 1990 as "widespread musculoskeletal pain for at least three months involving all four quadrants of the body, as well as the axial skeleton, and the presence of 11 or more out of 18 tender points on examination" (Wolfe et al., 1990). The PBAC noted a more recent definition but that the submission chose to use this definition.

The submission proposed that milnacipran be used after failure of standard therapy. Within the clinical treatment algorithm presented in the submission, milnacipran was considered as a second-line pharmacological treatment. Within this algorithm, patients commenced treatment with non-pharmacological therapy (education, physical activity and psychological therapy) and pharmacological treatment with a simple analgesic. Patients with inadequate response were then treated with a tricyclic antidepressant (amitriptyline). Patients with inadequate response or who were intolerant to tricyclic antidepressant treatment were then treated with a serotonin and noradrenaline reuptake inhibitor (SNRI) anti-depressant (milnacipran or duloxetine) or alpha-2-delta ligand anti-convulsant (pregabalin).

Milnacipran is the first drug approved in Australia by the TGA for the treatment of fibromyalgia. Current pharmacological treatment for fibromyalgia is most commonly off-label use of antidepressant medications; amitriptyline, duloxetine and pregabalin with many patients taking more than one medication for the treatment of fibromyalgia.

6. Comparator

Duloxetine was nominated in the submission as the main comparator presented in an indirect comparison to inform a cost-minimisation analysis. However, as duloxetine is not listed on the PBS for fibromyalgia, the submission used placebo as the comparator for the evaluation of cost-effectiveness. The submission also considered pregabalin to be a supplementary comparator for clinical evidence, but not for the economic analysis.

The PBAC considered that duloxetine was an appropriate comparator. Pregabalin was considered a minor comparator. The PBAC noted that both the sponsor's submission and the clinical expert at the hearing provided support for physical and psychological therapies being first line of treatment, followed by amitriptyline in those patients with an inadequate response. Duloxetine, milnacipran and pregabalin were alternative drug therapies if there was an inadequate response to amitriptyline. However the PBAC noted that clinical practice may change should milnacipran be PBS subsidised for fibromyalgia.

7. Clinical Trials

The submission presented a direct comparison based on five double-blinded randomised control trials (GE302, MD02, MD03, FMS031, FMS021) comparing milnacipran with placebo.

The submission also presented indirect comparisons of milnacipran, duloxetine and pregabalin using placebo as common comparator.

Details of the trials published at the time of submission are presented in the table below.

Trial ID/ First author	Publication title	Publication citation
Direct randomised trials		
Milnacipran vs placebo		
GE302 Branco J et al	A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia.	*J Rheumatol* (2010); 37(4): 851-9.
MD02 Clauw D et al	Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial.	*Clin Ther* (2008); 30(11): 1988-2004.
MD03 Arnold L et al	Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: results of a randomized, double-blind, placebo-controlled trial.	*Arthritis Rheum* (2010); 62(9): 2745-56.

Trial ID/ First author	Publication title	Publication citation
FMS021 Vitton O et al Gendreau R et al Harris R et al	 A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Efficacy of milnacipran in patients with fibromyalgia. Characterization and consequences of pain variability in individuals with fibromyalgia.	 *Hum Psychopharmacol* (2004); 19 Suppl 1: S27-35. *Journal of Rheumatology* (2005); 32(10): 1975-1985. *Arthritis and Rheumatism* (2005); 52(11): 3670-3674.
FMS031 Mease P et al	 The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial.	 *J Rheumatol* (2009); 36(2): 398-409.
Indirect comparisons (Common reference: Placebo)		
Duloxetine		
Arnold L	A double blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder.	*Athritis & Rheumatism* (2004); 50 (9): 2974-2984.
Arnold L	A randomized double-blind, placebo-controlled trial of Duloxetine in the treatment of women with or without major depressive disorder.	*Pain* (2005); 119: 5-15.
Russell I et al Mease P et al	Efficacy and safety of Duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed dose trial. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia.	*Pain* (2008); 136: 432-444. *Seminars in Arthritis and Rheumatism* (2010); 39(6): 454-464.
Chappell A et al Mease P et al	A six-month double-blind, placebo-controlled, randomized clinical trial of Duloxetine for the treatment of fibromyalgia. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia.	*Int J of General medicine* (2008); 1: 91-102. *Seminars in Arthritis and Rheumatism* (2010); 39(6): 454-464.

Trial ID/ First author	Publication title	Publication citation
Arnold L et al	Flexible dosed duloxetine in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled trial.	*J Rheumatol* (2010); 37(12): 2578-2586.
Arnold L et al	Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: Secondary analysis of a randomized, placebo-controlled trial.	*Arthritis Research and Therapy* (2011); 13(3).
Clauw D et al	Flexible dosed duloxetine versus placebo in the treatment of fibromyalgia: A randomized, double-blind trial.	*J of Pain* (2010); 11(4): S38.
Arnold L et al	Improvement in multiple dimensions of fatigue in fibromyalgia patients treated with duloxetine.	*Arthritis and Rheumatism* (2010); 62(105).
Pregabalin		
Crofford L	Pregabalin for the treatment of Fibromyalgia Syndrome. Results of a Randomized double-blind, placebo-controlled trial.	*Arthritis Rheum* (2005); 52(4): 1264-1273.
Mease P	A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia.	J Rheumatol (2008); 35(3): 502-514.
Arnold L	A 14-week, randomized, double-blinded, placebo-controlled Monotherapy trial of pregabalin in patients with fibromyalgia.	*J of Pain* (2008); 9(9): 792-805.
Pauer L	An international, randomized, double-blind, placebo-controlled, Phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia.	*J Rheumatol* (2011); 38(12): 2643-2652.
Crofford L	Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin.	*Pain* (2008); 136(3): 419-31.

The submission also considered four published meta-analyses to be of relevance, which included Derry et al 2012; Hauser et al 2011; Roskell et al 2011; and Smith et al 2011.

Details of the meta-analyses are presented in the table below.

Trial ID/First Author	Publication title	Publication citation
Milnacipran and duloxetine/pregabalin		
Hauser W et al	Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: A systematic review with meta-analysis.	*Rheumatology* (2011); 50(3): 532-543.
Roskell N et al	A meta-analysis of pain response in the treatment of fibromyalgia.	*Pain Practice* (2011); 11(6): 516-527.

Trial ID/First Author	Publication title	Publication citation
Milnacipran and duloxetine/pregabalin		
Smith B et al	Drug Class Review: Drugs for Fibromyalgia. Portland (OR): Oregon Health & Science University; April 2011	http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0010224/pdf/TOC.pdf.
Milnacipran only		
Derry S et al	Milnacipran for neuropathic pain and fibromyalgia in adults.	Cochrane Database of Systematic Reviews. (2012)

8. Results of Trials

The primary outcomes for the milnacipran vs. placebo trials were fibromyalgia pain (FM pain) and fibromyalgia syndrome (FM syndrome).

The primary outcomes for the duloxetine vs. placebo trials were the Brief Pain Inventory (BPI), Fibromyalgia Impact Questionnaire (FIQ total score and pain score), and Patient Global Impression of Improvement (PGI-I). The primary outcomes for the pregabalin vs. placebo trials were pain intensity on an 11 point scale (0 = no pain; 10 = worst possible pain).

For the indirect comparison, individual components from the primary composite outcomes and key secondary outcomes from the milnacipran trials were compared with relevant primary and secondary outcome measures from the duloxetine trials and the pregabalin trials.

The results of the primary outcomes of the direct comparison milnacipran trials with placebo at 14-18 weeks (FM pain and FM syndrome) are presented in the table below.

Trial	Miln n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95% CI)
FM pain responder at 3 months, ITT population, LOCF approach					
100 mg/day					
MD03	170/516 (32.9%)	97/509 (19.1%)	1.73 (1.39, 2.15)	13.9 (8.6, 19.2)	7 (5, 12)
MD02	103/399 (25.8%)	73/401 (18.2%)	1.42 (1.09, 1.85)	7.6 (1.9, 13.3)	13 (8, 53)
Pooled 100 mg/day			**1.59 (1.31, 1.93)**	**10.8 (4.7, 17.0)**	**9 (6, 21)**
200 mg/day					
GE302	104/430 (24.2%)	65/446 (14.6%)	1.66 (1.25, 2.20)	9.6 (4.4, 14.8)	10 (7, 23)
MD02	117/396 (29.5%)	73/401 (18.2%)	1.62 (1.25, 2.10)	11.3 (5.5, 17.2)	9 (6, 18)
Pooled 200 mg/day			**1.64 (1.36, 1.98)**	**10.4 (6.5, 14.3)**	**10 (7, 15)**
FM syndrome responder at 3 months, ITT population, LOCF approach					
100 mg/day					
MD03	117/516 (22.7%)	62/509 (12.2%)	1.86 (1.40, 2.47)	10.5 (5.9, 15.1)	10 (7, 17)
MD02	65/399 (16.3%)	39/401 (9.7%)	1.68 (1.15, 2.43)	6.6 (1.9, 11.2)	15 (9, 53)
Pooled 100 mg			**1.79 (1.43, 2.24)**	**8.5 (4.7, 12.4)**	**12 (8, 21)**
200 mg/day					
MD02	65/396 (16.4%)	39/401 (9.7%)	1.69 (1.16, 2.45)	6.7 (2.0, 11.3)	15 (9, 50)
Pooled 200 mg			**1.69 (1.16, 2.45)**	**6.7 (2.0, 11.3)**	**15 (9, 50)**

FM pain = VAS pain and PIGI; FM syndrome = VAS pain, PIGI and SF-36 PCS
Miln = milnacipran; PBO = placebo; ITT = intention to treat population; LOCF = last observation carried forward; NNT = number needed to treat; RR = relative risk; RD = risk difference; CI = confidence interval

The results showed statistically significant differences between milnacipran and placebo for both FM pain and FM syndrome for both 100 mg/day and 200 mg/day milnacipran, however, the response rate for milnacipran compared with placebo was small. The response rate for FM syndrome was lower than for FM pain, meaning the number needed to treat for FM

syndrome was higher (NNT: 12; 95% CI: 8, 21) compared with FM pain (NNT: 9; 95% CI: 6, 21). Milnacipran 200 mg/day did not appear to be more effective than 100 mg/day for either FM pain or FM syndrome.

The adjusted mean difference for the key secondary outcomes in the milnacipran trials at three months, using LOCF methodology are presented below.

Outcome	100 mg vs PBO (MD03, MD02, FMS031)	200 mg vs PBO (GE302, MD02, FMS031, FMS021)
	MD 95% CI	MD 95% CI
VAS pain (0-100)	-4.40 (-7.29, -1.50)	-4.57 (-6.29, -2.86)
BPI (0-10)	-0.65 (-0.90, -0.40)	-0.44 (-0.69, -0.19)
PGIC (0-7)	-0.46 (-0.57, -0.35)	-0.41 (-0.53, -0.29)
SF-36 PCS (0-100)	1.37 (0.76, 1.97)	0.85 (0.27, 1.43)
SF-36 MCS (0-100)	1.50 (0.55, 2.45)	1.55 (0.80, 2.31)
FIQ total score (0-100)	-4.48 (-6.22, -2.73)	-2.99 (-4.53, -1.45)

LOCF = last observation carried forward; VAS = visual analogue scale; BPI = Beck Pain Inventory; PGIC – Patient Global Impression of Change; SF-36 = Short Form-36 Health Survey; PCS = Physical Component Score; MCS = Mental Component Score; FIQ = Fibromyalgia Impact Questionnaire;

Pooled results showed a statistically significant difference for all secondary outcomes between both milnacipran doses and placebo. However, the mean difference for milnacipran compared with placebo was small.

The results of the indirect comparison between milnacipran (100 mg/day) and duloxetine (30 mg, 60 mg and 60-120 mg/day) are presented in the table below. As the maximum recommended dose of duloxetine is 60 mg, an analysis of the data using 60 mg or less of duloxetine was performed. A summary of the results are shown in the table below.

Outcome	Miln 100 mg vs. PBO	Dul (30-120 mg) vs. PBO	Indirect comparison	
			Miln 100 mg vs. Dul (30-120 mg)	Miln 100 mg vs. Dul (≤60 mg) [a]
	RD (95% CI)	RD (95% CI)	MD (95% CI)	MD (95% CI)
≥30% reduction in pain [b]	**9.7% (4.4%, 14.9%)**	**13.3% (6.9%, 19.7%)**	-3.6% (-11.9%, 4.6%)	-8.4 (-18.3, 1.5)
	MD (95% CI)	MD (95% CI)		
BPI – average pain severity	**-0.65 (-0.90, -0.40)**	**-0.70 (-0.95, -0.45)**	0.05 (-0.30, 0.40)	0.07 (-0.48, 0.62)
FIQ total score	**-4.48 (-6.22, -2.73)**	**-5.01 (-7.07, -2.95)**	0.53 (-2.17, 3.23)	1.72 (-0.92, 4.36)
MFI general fatigue	-0.26 (-0.52, 0.00)	-0.43 (-0.95, 0.09)	0.17 (-0.41, 0.75)	0.06 (-0.21, 0.33)
SF-36 PCS	**1.37 (0.76, 1.97)**	**1.22 (0.36, 2.08)**	0.15 (-0.90, 1.20)	0.21 (-0.54, 0.96)
PGIC/PCI-I	**-0.46 (-0.57, -0.35)**	**-0.41 (-0.58, -0.24)**	-0.05 (-0.25, 0.15)	-0.09 (-0.20, 0.02)
SF-36 MCS	**1.50 (0.55, 2.45)**	**3.08 (2.03, 4.14)**	**-1.58 (-3.00, -0.16)**	**-2.09 (-3.54, -0.64)**

Miln = milnacipran; Dul = duloxetine; PBO = placebo; BPI = Brief pain inventory; FIQ = fibromyalgia impact questionnaire; MFI = Multi-dimensional Fatigue Inventory; SF-36 = Short Form 36; PCS = Physical component score; MCS = Mental component score; PGIC = Patient Global Impression of Change; PGI-I = Patient Global Impression – Improvement; VAS = visual analogue scale; **Bold** = statistically significant

[a] Includes Arnold 2005 (60 mg/day), Russell 2008 (60 mg/day) and HMGG (30 mg/day)

[b] Pain VAS for milnacipran trials and BPI average pain severity for duloxetine trials

The indirect comparison, including duloxetine doses of less than or equal to 60 mg/day showed that milnacipran is non-inferior to duloxetine for most outcomes using placebo as the common comparator.

The results of the indirect comparison between milnacipran (100 mg/day) and pregabalin (300 mg and 450 mg/day) are presented in the table below.

Outcome	Miln vs. PBO	Pregabalin vs. PBO	Miln vs. Pregabalin
Milnacipran 100 mg/day vs pregabalin 300 mg/day			
	RD (95% CI)	***RD (95% CI***	***RD (95% CI)***
Pain, 30% responder [a]	**9.7% (4.4%, 14.9%)**	**11.2% (6.3%, 16.1%)**	-1.5% (-8.7%, 5.7%)
PGIC responder	**11.6% (6.3%, 16.8%)**	**9.9% (4.6%, 15.2%)**	1.7% (-5.8%, 9.2%)
	MD (95% CI)	**MD (95% CI)**	**MD (95% CI)**
SF-36 PCS	**1.37 (0.76, 1.97)**	0.12 (-1.40, 1.64)	1.25 (-0.39, 2.89)
SF-35 MCS	**1.50 (0.55, 2.45)**	0.67 (-1.52, 2.86)	0.83 (-1.56, 3.22)
FIQ total score	**-4.48 (-6.22, -2.73)**	**-2.19 (-4.29, -0.08)**	-2.29 (-5.02, 0.44)
MFI global	**-1.85 (-2.85, -0.84)**	-2.11 (-4.61, 0.39)	0.26 (-2.08, 2.60)
Milnacipran 100 mg/day vs. pregabalin 450 mg/day			
	RD (95% CI)	**RD (95% CI**	**RD (95% CI)**
Pain, 30% responder [a]	**9.7% (4.4%, 14.9%)**	**15.5% (10.0%, 20.9%)**	-5.8% (-13.4%, 1.8%)
PGIC responder	**11.6% (6.3%, 16.8%)**	**16.4% (7.0%, 25.9%)**	-4.8% (-15.6%, 6.0%)
	MD (95% CI)	**MD (95% CI)**	**MD (95% CI)**
SF-36 PCS	**1.37 (0.76, 1.97)**	0.79 (-0.72, 2.30)	0.58 (-1.05, 2.21)
SF-35 MCS	**1.50 (0.55, 2.45)**	1.53 (-0.63, 3.69)	-0.03 (-2.39, 2.33)
FIQ total score	**-4.48 (-6.22, -2.73)**	**-4.38 (-6.69, -2.07)**	-0.10 (-3.00, 2.80)
MFI global	**-1.85 (-2.85, -0.84)**	**-2.30 (-4.28, -0.33)**	0.45 (-1.77, 2.67)

Miln = milnacipran; PBO = placebo; FIQ = fibromyalgia impact questionnaire; MFI = multidimensional fatigue inventory SF-36 = Short Form 36; PCS = Physical component score; MCS = Mental component score; MD = mean difference; RD = risk difference; CI = confidence interval; PGIC = Patient Global Impression of Change; **bold** = statistically significant.

[a] Pain visual analogue scale in the milnacipran trials and Pain numerical rating scale in pregabalin trials

For PBAC's view, see Recommendation and Reasons.

The most frequently reported treatment related adverse events in the milnacipran 100 mg/day and 200 mg/day that resulted in statistically significant differences compared with placebo were nausea, headache, constipation, dizziness, insomnia, hyperhidrosis, palpitations, tachycardia, hypertension, increased blood pressure and heart rate and vomiting.

Adverse events were more commonly reported as a reason for discontinuation in the milnacipran arms of the trials: the risk difference is statistically significant for milnacipran 100 mg (RD 0.08 (0.03, 0.12)) and milnacipran 200 mg (RD 0.14 (0.11, 0.17)).

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described milnacipran as superior in terms of comparative effectiveness and equivalent in terms of comparative safety with placebo.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis based on non-inferior efficacy and safety of milnacipran compared with duloxetine. As duloxetine is not listed on the PBS for the treatment of fibromyalgia, the submission also presented a cost-effectiveness evaluation for milnacipran based on the claim of superior effectiveness and equivalent safety compared with placebo. The submission presented an incremental cost-effectiveness ratio (ICER) of between $15,000 and $45,000 per quality adjusted life years gained (QALY), which was based on converting SF-36 results to SF-6D from the clinical trials at three months and extrapolating to one year. The submission did not present an economic analysis against pregabalin.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost per year of milnacipran to the PBS to be less than 10 million per year in year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered that duloxetine was an appropriate comparator. Pregabalin was considered a minor comparator. The PBAC noted that both the sponsor's submission and the clinical expert at the hearing provided support for physical and psychological therapies being first line of treatment, followed by amitriptyline in those patients with an inadequate response. Duloxetine, milnacipran and pregabalin were alternative drug therapies if there was an inadequate response to amitriptyline. However the PBAC noted that clinical practice may change should milnacipran be PBS subsidised for fibromyalgia.

The PBAC raised a number of concerns about the proposed restriction. The limitation to a specialist 'qualified to diagnose' is problematic. The PBAC agreed that this condition was often, but not always, diagnosed by a rheumatologist. It is doubtful if the Department of Human Services (formerly Medicare Australia) would be able to accurately confirm prescription only by this specialists group. Failure of 'standard therapy' was not clearly defined. The PBAC considered that standard therapy could be considered as non-pharmacological (physical and psychological therapies) and this view would lead to milnacipran being considered as one of a number of first-line pharmacological options including amitriptyline.

While noting the sponsor's proposed restriction to diagnostic criteria containing tender point examination, which was considered common practice by the clinician at the hearing, the criteria for classification of fibromyalgia have recently changed. Therefore a number of clinicians may rely on severity of specific symptoms without the additional criteria of 11 of 18 tender points. This was considered likely to increase the number of people diagnosed by 10 to15%. PBAC also considered that ongoing management of fibromyalgia is most likely to be undertaken by general practitioners who will decide, in consultation with patients, if there has been a benefit.

The PBAC considered the indirect comparison of duloxetine (at doses less than 60 mg daily) and milnacipran 100 mg was informative, as were the trials comparing milnacipran and

placebo. The comparison with pregabalin was less informative. The effect size for milnacipran compared to placebo in the trials presented in the submission was modest although statistically significant. The PBAC agreed with its Economic Subcommittee (ESC) that a reduction of 30% in pain scores was indicative of a small benefit. The PBAC noted that ESC considered the LOCF (last observation carried forward) method could overestimate the effect of milnacipran. The PBAC noted the high and differential numbers of patients discontinuing in the arms of the clinical trials could lead to overestimation by the LOCF method but noted the BOCF (baseline observation carried forward) method provided some confidence that the overestimation was not substantial.

The indirect comparison at the appropriate doses of duloxetine (less than 60 mg per day) showed non-inferiority for most of the outcomes measured except SF-36 MCS (SF-36 mental component score). The differences between the trials of milnacipran and duloxetine were important: particularly in different extent of antidepressant use in trials for each drug, and that patients were not non-responders to amitriptyline. The proportion of patients with current major depressive episodes was 16.7% - 40.8% in the duloxetine trials but was not reported in the milnacipran trials although the SF-36 MCS were similar at initiation. As milnacipran is an antidepressant and major depression is a high but frequently unrecognised component of patients presenting with pain, comparability of the results is problematic.

Overall, the PBAC considered the applicability of the studies to the Australian population was poor. Fibromyalgia is a complex, relapsing and remitting condition where symptoms fluctuate in intensity and patients may cycle through different therapies over time. The PBAC noted that trial populations were 92% Caucasian and considered that in an Australian population, cultural factors may influence the presentation of depression and some chronic pain conditions.

The PBAC noted that adverse events were reported more frequently in the milnacipran arm of the trials and were a common reason for discontinuation. The PBAC accepted the ESC advice regarding the number needed to harm (7 to 14) with milnacipran was similar to the number needed to treat (9 to 12). The PBAC also considered that discontinuation syndrome was likely to be associated with milnacipran for a proportion of patients.

The claim of non-inferiority of milnacipran with duloxetine was not supported by the data presented in the submission. Therefore the cost minimisation analysis was not accepted by the PBAC.

The claimed superiority in terms of comparative efficacy of milnacipran to placebo was small and uncertain. Therefore the cost effectiveness analysis was also uncertain. In addition the PBAC considered that extrapolation of the results of the milnacipran effect size from 3 months in the trials to 12 months was problematic. Given the normal fluctuations of this condition the trial duration is unlikely to have been sufficient to include these fluctuations in the estimate of effect size.

The PBAC noted that the QALY gain is minimal. The utility difference, based on an assumption of continued effectiveness is only 0.02 QALYs. The PBAC considered that this claim was not adequately supported given the high withdrawal rates of the trials. The PBAC also considered the model structure simplistic and unlikely to reflect clinical practice.

The PBAC considered the utilisation and financial cost are likely to be underestimated and the submission's estimate of 2% prevalence likely to be low. The publication of amended diagnostic criteria for fibromyalgia could be a factor in greater incidence of cases of fibromyalgia, owing to differences between the two versions. The PBAC agreed with its Drug Utilisation Subcommittee (DUSC) that the discontinuation proposed in the submission may not recognise the potential for a proportion of patients to persist with treatment in spite of marginal benefit. The PBAC noted that fibromyalgia is a condition was with high clinical need and very few effective treatments. The listing of a treatment specifically indicated for fibromyalgia was considered likely to drive initial uptake to a greater extent than estimated in the submission.

Given the fluctuations and cycling through therapies that is common in conditions such as fibromyalgia the uptake of therapy in the first year may be underestimated but could be overestimated in later years.

PBAC agreed with DUSC that there were a number of important Quality use of Medicines matters associated with listing milnacipran. Of particular concern was the potential for misunderstanding by prescribers of the pharmacology of milnacipran and inappropriate use with another antidepressant.

The PBAC therefore rejected the submission on the basis of high uncertainty in the clinical claim of non-inferiority with duloxetine and a small benefit and uncertain cost effectiveness compared to placebo.

Recommendation:
Reject

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

Pierre Fabre Medicament Australia is committed to continuing to work with the PBAC in order to achieve PBS listing for milnacipran in fibromyalgia.