REQUEST FOR ACM ADVICE

ACM Meeting **2020/4; ACM 22**

Submission number N/A

Agenda Item and Title **3.1 Pharmacovigilance matter for advice – Antidepressants (SSRIs and SNRIs) and youth suicide**

Medicine	Selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors	
Sponsor(s)	**Selective Serotonin Reuptake Inhibitors (SSRIs)**	
	Citalopram (Cipramil)	Lundbeck Australia Pty Ltd
	Dapoxetine (Priligy)	A Menarini Australia Pty Ltd
	Escitalopram (Lexapro)	Lundbeck Australia Pty Ltd
	Fluoxetine (Prozac)	Eli Lilly Australia Pty Ltd
	Fluvoxamine (Luvox)	Mylan Health Pty Ltd
	Paroxetine (Aropax)	Aspen Pharmacare Australia Pty Ltd
	Sertraline (Zoloft)	Upjohn Australia Pty Ltd
	Serotonin and Noradrenaline Reuptake Inhibitors	
	Desvenlafaxine (Pristiq)	Pfizer Australia Pty Ltd

	Duloxetine (Cymbalta)	Eli Lilly Australia Pty Ltd
	Milnacipran (Jonica)	Pierre Fabre Australia Pty Ltd
	Venlafaxine (Efexor)	Upjohn Australia Pty Ltd
Indication	**Selective Serotonin Reuptake Inhibitors (SSRIs)**	
	Citalopram	• Major depression
	Dapoxetine	• Premature ejaculation in men aged 18 to 64 years
	Escitalopram	• Major depression • Social anxiety disorder (social phobia) • Generalised anxiety disorder • Obsessive compulsive disorder
	Fluoxetine	• Major depression • Obsessive compulsive disorder • Pre-menstrual dysphoric disorder
	Fluvoxamine	Children and Adolescents (8 years and over) • Obsessive compulsive disorder Adults • Major depression • Obsessive compulsive disorder
	Paroxetine	• Major depression and prevention of relapse of depressive symptoms • Obsessive compulsive disorder and prevention of its relapse • Panic disorder and prevention of its relapse • Social anxiety disorder • Generalised anxiety disorder • Post-traumatic stress disorder
	Sertraline	Children and Adolescents (6 years and over) • Obsessive compulsive disorder Adults • Major depression

		• Obsessive compulsive disorder • Panic disorder • Social phobia and prevention of its relapse • Pre-menstrual dysphoric disorder
	Serotonin and Noradrenaline Reuptake Inhibitors	
	Desvenlafaxine	• Major depressive disorder, including the prevention of relapse • "Not indicated for paediatric use"
	Duloxetine	• Major depressive disorder • Diabetic peripheral neuropathic pain • Generalised anxiety disorder
	Milnacipran	• Management of fibromyalgia
	Venlafaxine	• Major depression, including prevention of relapse and recurrence • Generalised anxiety disorder • Social anxiety disorder • Panic disorder, including prevention of relapse
Summary of Issues	A recent review article on the issue of antidepressants and youth suicide in the journal Frontiers in Psychiatry (1), identified a signal from ecological evidence correlating an increase in dispensing of antidepressants in young Australians aged less than 28 years and increased suicidality or self-harm in young Australians aged less than 25 years. Although there are significant uncontrolled confounding factors that limit the interpretation of this conclusion, the article has prompted further TGA consideration of this issue. Clinical worsening of depression and suicidality is a recognised and well-known risk with the use of antidepressant medicines and the TGA approved Product Information (PI) documents for antidepressants include warnings about these risks and specifically mention children, adolescents and young adults. This information is also conveyed in the Consumer Medicines Information (CMI) for these products. Whilst some SSRIs are indicated in children for the treatment of obsessive compulsive disorder, SSRIs and SNRIs may be prescribed off-label to children and adolescents for other psychiatric indications. For example, fluoxetine is recommended by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) as second line treatment for moderate to severe major depressive disorder in children and adolescents (2). However, the Product Information for fluoxetine states that use in patients under the age of 18 years is not recommended. A joint clinical guidance document (2) on the use of antidepressant medications in children and adolescents (issued by RANZCP, the Royal	

	Australian College of General Practitioners (RACGP), and the Royal Australasian College of Physicians (RACP)) is currently under review. The current RANZCP clinical practice guidelines for mood disorders (3) state that two recent Cochrane reviews address the treatment of major depression in children and adolescents, both highlighting significant methodological limitations of the available literature. The first Cochrane review (4) focuses on newer generation antidepressant medications (SSRIs, SNRIs, norepinephrine dopamine reuptake inhibitors (NDRIs), norepinephrine dopamine disinhibitors (NDDIs) and tetracyclic antidepressants (TeCAs)), and found Level I evidence for a small beneficial effect of SSRIs in the treatment of depressive disorders amongst children and adolescents aged 6–18 years. The same review also highlighted the increased risk (58%) of suicidal behaviours and suicidal ideation amongst those receiving antidepressants relative to placebo. Although there were no completed suicides in any of the trials included in this Cochrane review, none of the included trials had adequate power for robust safety analyses. The RANZCP guidelines also state that of the SSRIs, fluoxetine has the most consistent evidence of efficacy over placebo, and is recommended as the first line antidepressant for young people in the UK National Institute for Health and Care Excellent (NICE) treatment guidelines (5). In addition, a highly cited systematic review concluded that the efficacy of antidepressants correlates with depression severity, and that the benefits over placebo are substantial for severe symptoms, but minimal or non-existent with mild-moderate depression (6). Clinical advice is sought from the ACM to assist the TGA in clarifying the current role of SSRIs and SNRIs in treating psychiatric disorders amongst children, adolescents and young adults and determining whether current Australian risk minimisation measures are sufficient to inform prescribers of the potential risk of increased suicidality in children and adolescents who are prescribed SSRIs or SNRIs.
Advice sought	The committee is requested to provide advice on the following specific issues: 1. Can the committee comment on the current role of SSRIs and SNRIs in clinical practice in Australia for treating psychiatric disorders and developmental disorders in children, adolescents and young adults? 2. Can the committee comment on the strength of the current evidence for an association between use of antidepressants and rates of youth suicide in Australia? 3. Can the committee comment on whether additional risk minimisation measures are warranted and would be effective to address any potential risk of suicide amongst children, adolescents and young adults prescribed SSRIs or SNRIs? Examples of additional risk minimisation measures could include:

	• Narrowing of indications to specify an age-range (e.g. treatment of major depression in adults aged over x years). • Strengthening existing warnings and precautions. • Making an application to amend the Poisons Standard to include of SSRIs/SNRIs in Appendix D, to specify which types of medical practitioners can prescribe these medications to children and adolescents (e.g. only paediatricians and psychiatrists). • Referral to the Pharmaceutical Benefits Advisory Committee for consideration of changes to PBS prescribing conditions (e.g. to exclude children or adolescents or to require an authority to prescribe to children). • Additional prescriber education. • Additional consumer education.
Attachments	1. Whitely M, Raven M & Jureidini. Antidepressant Prescribing and Suicide/Self-Harm by Young Australians: Regulatory Warnings, Contradictory Advice, and Long-Term Trends. Frontiers in Psychiatry. 2020;11:478 (TRIM D20-983523) 2. RANZCP, RACGP & RACP. Clinical guidance on the use of antidepressant medications in children and adolescents. March 2005. (TRIM D20-999266) 3. Malhi G, Bassett D, Boyce P, et al. A. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand Journal of Psychiatry, 2015;49(12): 1-185 (TRIM D20-987614) 4. Hetrick SE, McKenzie JE, Cox GR et al. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews, 2012;11 (TRIM D20-988764). 5. National Institute for Health and Care Excellence (NICE). Depression in Children and Young People: Identification and Management in Primary, Community and Secondary Care, 2005 (TRIM D20-988765). 6. Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity: A patient-level meta-analysis. Journal of the American Medical Association, 2010; 303:47-53 (TRIM D20-988767).

Dr Claire Behm [electronically signed] 7 July 2020

Delegate of the Secretary under regulation 35A of the *Therapeutic Goods Regulations 1990*

Date