Document 1

Australian Government
Department of Health

Information Brief
MB20-003171
Date sent to MO: 16/09/20

To: **Minister Hunt**
cc: **Minister Colbeck; Minister Coulton**

Subject: **INFORMATION BRIEF: ANTIDEPRESSANTS AND YOUTH SUICIDE**

Minister Hunt …… **Date:** / /			
Comments:			
Contact Officer:	*Elspeth Kay*	*A/g Assistant Secretary, Pharmacovigilance and Special Access Branch, Medicines Regulation Division*	Ph: (02) 6289 3528 Mobile: s22 [redacted]
Clearance Officer:	*Adj Prof John Skerritt*	*Deputy Secretary, Health Products Regulation Group*	Ph: (02) 6289 4200 Mobile: s22 [redacted]

Key Issues:

1. The Therapeutic Goods Administration (TGA) is reviewing the issue of antidepressants and youth suicide following the June 2020 publication of a review article in Frontiers in Psychiatry by Whitely et al that proposed a causal relationship between antidepressant prescribing and youth suicide.
2. The preliminary findings of the TGA review do not support the conclusions that increased rates of antidepressant prescribing are contributing to increased rates of youth suicide.
3. To date the TGA has critically analysed the Whitely et al paper, performed a statistical analysis of Pharmaceutical Benefits Scheme (PBS) and Australian Bureau of Statistics (ABS) data and has sought advice from the Advisory Committee on Medicines (ACM). The TGA will undertake further data analysis and correspond with relevant medical colleges regarding the production of prescriber education materials and clinical guidelines, before finalising and publishing the review outcomes.

Background:

Temporary clinical worsening of depression and suicidality is a rare but well-known risk with the use of antidepressant medicines. The Product Information (PI) and Consumer Medicine Information (CMI) documents for all antidepressants registered in Australia contain warnings about these risks and specifically mention children, adolescents and young adults. The TGA has previously published multiple risk communications in relation to this issue.

A recent review article published in *Frontiers in Psychiatry* by Martin Whitely (John Curtin Institute of Public Policy, Curtin University) and Melissa Raven and Jon Jureidini (Critical and Ethical Mental Health Research Group, University of Adelaide) has prompted further TGA consideration of youth suicide and antidepressants.

TGA Review:

The TGA has conducted a critical analysis of the Whitely et al paper, undertaken a more detailed analysis of PBS and ABS data and sought expert advice from the ACM.

Critical analysis of Whitely et al

Whitely et al presented an analysis of PBS and ABS data that correlated an increase in PBS dispensing of antidepressants in Australians aged less than 28 years and an increasing rate of suicide in Australians aged less than 25 years from 2008–2018. Correlation does not prove causation. The TGA's critical analysis of the Whitely et al paper has identified a number of deficiencies in the paper, namely:

1. Interpretation of the association between antidepressant dispensing and suicide is highly confounded by the nature of the condition being treated (referred to as confounding by indication). Youth with severe symptoms of depression, who will already be at a higher risk of suicide, are more likely to be managed with medication than youth with mild or no symptoms of depression.
2. The article does not account for the significant confounding factors that contribute to the complex outcome of suicide, such as drug and alcohol use, cyber bullying, school and family dynamics.
3. Male and female rates of youth suicide were not analysed separately despite well-established sex differences in suicide risk.
4. Whitely et al juxtaposed the rates of suicide (per 100 000) with the rates of antidepressant dispensing (per 100) in one graph, essentially multiplying the former by a factor of 1000 and creating a distorted picture of rising antidepressant dispensing on the PBS and rising rates of suicides.

Analysis of PBS data

To explore the potential for differences in antidepressant dispensing and rates of youth suicide in males and females, the TGA performed an additional analysis of PBS and ABS data. This analysis found that in not reviewing suicide rates independently for each sex, Whitely et al overlooked different trends between males and females and a slow-down or reversal in suicide rates in more recent years, despite ongoing increases in antidepressant dispensing. The analysis found that:

- Male suicide rates increased from 2009 to 2018 by 33 per cent, but with a smaller increase of 10 per cent from 2013–2015 to 2016–2018, compared with an increase of 20 per cent from 2009–2012 to 2013–2015.
- Female suicide rates increased by 9 per cent over the same time period, but the trend reversed in the latter half of the ten-year period, with a decrease of 4 per cent from 2013–2015 to 2016–2018, compared with an increase of 14 per cent in the earlier years.
- Over the same period, antidepressant prescribing increased similarly for both males and females under 25 years.
- Thus, despite a universal increase in antidepressant dispensing, male and female suicide risks have experienced diverging and contrary trends.

ACM Advice

The TGA sought advice from the ACM on 7 August 2020. In addition to Professor s22 s22 a psychiatrist who is a permanent member of the ACM, two additional experts nominated by the ACM Chair were invited to participate in the item. The two invited experts were Paediatrician/Associate Professor in Paediatrics s22 and Child and Adolescent Psychiatrist/Public Health Physician Dr s22. The ACM provided the following advice:

- the committee did not support the conclusion drawn by Whitely et al
- the Whitely et al paper has not materially affected the current evidence for an association between the use of antidepressants and rates of youth suicide in Australia
- there is a valid and important role for selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors antidepressants in current clinical practice, supported by professional guidelines
- the increasing use of antidepressants in children is of concern. Current clinical guidelines have a strong emphasis on psychosocial therapies as the preferred mode of treatment for depressive disorders in children and adolescents, with the use of antidepressants reserved for moderate-to-severe depression when other treatments have failed
- in practice, access to publicly funded psychological therapies such as cognitive behavioural therapy and interpersonal therapy is often extremely limited, GPs face great difficulty in having their patients seen by a child/adolescent psychiatrist in a timely manner, referral pathways are complex and there are significant equity issues in accessing private psychiatric services
- activation syndrome is recognised and includes the possible emergence of suicidal thoughts during the initial few months of antidepressant treatment or at times of dose adjustments. The risk is minimised by starting with a low dose and increasing slowly
- further prescriber and consumer educational material is required, especially regarding appropriate dosing in the paediatric and adolescent populations

- any regulatory action to limit prescriber or PBS eligibility criteria is not justified on the strength of the current evidence and would further disadvantage children and adolescents, especially in regional, rural and remote areas where access to specialists and psychological therapies is limited.

Stakeholder engagement:

The TGA have liaised with the Technology Assessment and Access Division and Deputy CMO Dr Ruth Vine on this issue.

On 24 August 2020, the authors of the review article, Professor Jon Jureidini, Dr Melissa Raven and Dr Martin Whitely, wrote to the TGA restating their position on this issue and requesting to be involved in the review. Julian Hill MP wrote to you directly on 26 August 2020 requesting assurance that external specialist input to the TGA review will be considered.

Planned next steps:

Further work is required prior to completion of the review and publication of the outcomes. This will include:

- further collaboration with Technology Assessment and Access Division to perform additional data analyses
- referring the issues raised by the ACM with respect to equity of access to psychological and psychiatric care for young Australians to the Primary Care & Mental Health Division
- correspondence with relevant medical colleges, including the Royal Australian College of General Practitioners and the Royal Australian and New Zealand College of Psychiatrists, regarding the production of prescriber education material and clinical guidelines.

Attachments:

Attachment A TGA data analysis

PDR No:	MB20-003171
Subject:	Information Brief: Antidepressants and youth suicide
Division	Medicines Regulation
MO Action Date	14 September 2020

OFFICIAL

Australian Government
Department of Health

Event / Meeting Brief
MB21-002345
Version (1)
Date sent to MO: 28/07/21

To: Minister Hunt

Subject: MEETING BRIEF - DR ANNE ALY MP

Minister Hunt Signed ……. **Date: / /**			
Comments:			
Contact Officer:	*Dr Jane Cook*	*First Assistant Secretary, Medicines Regulation, Health Products Regulation Group*	Ph: (02) 6289 4210 Mobile: s22 [redacted]
Clearance Officer:	*Adj Prof John Skerritt*	*Deputy Secretary, Health Products Regulation Group*	Ph: (02) 6289 4200 Mobile: s22 [redacted]

Date / Time: 2 August 2021, 7.00pm -7.15pm

Meeting Type/Location: APH – M1.41

Traditional Custodians: Ngunawal

Purpose: To discuss the format and content of Consumers Medicines Information (CMI) in light of claims that pharmaceutical companies are inappropriately excluding information on certain side effects.

Desired Outcomes: For Dr Aly to understand the circumstances regarding the use of CMIs in Australia and why the information in them is deliberately not as comprehensive and detailed as the Product Information intended for health professionals to use. Also to explain that there are no powers in law that enable the government or the TGA to approve the content of individual CMI documents.

Key Attendees/Speakers:	**Title:**	**Organisation:**	**Mobile No:**
Dr Anne Aly MP	Dr	Australian Labor Party	unknown

Key Matters:

1. The Member for Cowan, the Hon Dr Anne Aly MP, has been contacted by Mr s22 [redacted], a self-described advocate for reform in mental health support services, who has alleged that pharmaceutical companies have breached the Therapeutic Goods Regulations by excluding information on certain side effects from the Consumer Medicines Information (CMI) documents.

2. Mr s22 [redacted] does not accept that Australian CMIs are not intended to contain information at his preferred level of detail nor that no breach of regulations has occurred. He has corresponded with multiple bodies (**Attachment A**) and unsuccessfully referred TGA to the Australian Human Rights Commission.

3. CMIs are intended to notify patients and carers of the most relevant information and direct them back to health professionals, if necessary, for discussion and more detailed information tailored to their circumstances. The CMI is not a replacement for the discussion between a patient and their health care professional (pharmacist or doctor).

4. Anyone wanting the full information about a product can download the Product Information (PI) documents from the TGA website.

5. A simpler CMI format was introduced in 2019, following extensive consultation and testing with industry, health professionals and consumers. The new template is shorter, better laid-out and features a one-page summary that provides people with the most critical information about their medicine at a glance.

6. Following the introduction of the simpler CMI format, many pre-existing CMIs are being updated much earlier than the December 2025 transition deadline. As part of the opioid reforms, for example, all innovator product CMIs have already been updated with additional warnings, and all generic CMIs will be completed by the end of 2021.

7. The TGA is currently undertaking a review of the quality of benzodiazepine CMIs which includes reviewing the information provided to patients on topics such as drug interactions, addiction, and dependence.

8. It has been suggested by both Mr s22 [redacted] and Dr Aly that Australian CMIs could simply cut and paste the extensive warnings contained with equivalent documents regulated by the FDA. This is a misunderstanding of the intended purpose of CMIs in Australia and their place in interactions between health professionals and consumers.

9. Overseas equivalents to CMIs may not necessarily provide the most relevant information to consumers in the most suitable format, do not address the context of medicines in use in the Australian clinical situation and in the USA are also partly used as a shield against litigation with far more detail about serious, but rare, risks than is useful for most consumers.

10. The Therapeutic Goods Regulations have not been breached and pharmaceutical companies have not acted illegally in not listing all possible side effects in the CMI.

Stakeholder information / Biography:

- Federal Member for Cowan, Dr Anne Aly MP
  Deputy Chair of Parliamentary Joint Committee on Law Enforcement
  Australian Labor Party

- The Minister recently responded to correspondence from Dr Aly (MC21-019651) on the matter of CMIs for prescribed medications.

Proposed Objective and/or Desired Outcomes:

- To explain to Dr Aly the circumstances regarding the use of CMIs in Australia, and why the information in them is deliberately not as comprehensive and detailed as the PIs intended for health professionals to use.

Stakeholder Objective:

- Dr Aly is likely to:
  - ask that Minister Hunt meet two activists, Mr s22 and Mr s22 s22
  - suggest that Australian CMIs include lengthy warnings contained within their US equivalents;
  - suggest that the transition period to the updated CMI format is too long for pre-existing products (required by December 2025);
  - discuss the death of s22, covered in a 7.30 Report item, as an example of the claimed need for changes to CMIs.

Key Points:

- Australian CMIs are not intended to contain exhaustive information. They aim to notify patients and carers of the most relevant information and direct them back to health professionals for relevant detailed information.
- Anyone wanting the full information about a product can download the PI documents from the TGA website. However, interpreting PIs usually requires a significant level of health literacy.
- Overseas equivalents to CMIs may not necessarily be to provide the most relevant information to consumers in the most suitable format, but also be used partly as a shield against litigation with far more detail about serious, but rare, risks than is useful for most consumers.
- Many pre-existing CMIs are being updated much earlier than the December 2025 deadline. As part of the opioid reforms, for example, all innovator CMIs have already been updated with additional warnings, and generic CMIs will be completed by the end of 2021.
- The TGA is currently undertaking a review of the quality of benzodiazepine CMIs that includes reviewing the information provided to patients on topics such as drug interactions, addiction, and dependence.
- Regarding the tragic passing of s22 [redacted], the factors in his death are complex, involving interactions with a range of health professionals and, at this stage, it is not clear what influence any form of written patient information could have had on his situation.

Sensitivities or Contentious Issues:

- The ABC's 7.30 Report has aired a story regarding s22 [redacted] www.abc.net.au/7.30/calls-to-improve-warnings-about-the-deadly-risks/13330996

Budget/Financial Implications:

- None.

Attachments:

A. History of correspondence

Minister	**Minister Hunt**
PDR Number	**MB21-002345**
Subject	Meeting Brief - Dr Anne Aly MP
Due Date	28 July 2021
Quality Assurance Check (completed by line area)	s22 [redacted]
Contact Officer	Dr Jane Cook (02) 6289 4210 s22 [redacted]
Clearance Officer	Adj Prof John Skerritt (02) 6289 4200 s22 [redacted]
Division/Branch	|Health Resourcing| Medicines Regulation

Adviser/DLO Comments:

Return to Dept for:

Redraft ☐

Attachment A

History of correspondence

Correspondence between Mr s22 and TGA

- Head of the TGA Adj Prof John Skerritt received a letter from Mr s22 on 9 July 2020, together with a copy of the report entitled 'Prescribed Deaths – Life in the Killing Zone'.
- Mr s22 was particularly concerned about what he perceived as non-disclosure of side effects in the CMIs for opioid, antidepressant, antipsychotic, stimulant and anxiolytic medicines.
- Adj Prof John Skerritt sent a response to Mr s22 on 23 July 2020. In this letter, he stated that while the CMI are required by the Therapeutic Goods Regulations 1990 to be consistent with the PI, they are not required to contain exactly the same content.
- Mr s22 replied to Professor Skerritt's letter on 4 August 2020. The second letter did not present new arguments, the arguments had been addressed in the original TGA response, and we did not believe at the time that further communication would satisfy Mr s22 concerns.
- Mr s22 wrote a lengthy third letter titled 'Professor Skerritt Complaint Relodgement 1st November 2020' containing large excerpts from his report with associated questions. Adj Prof Skerritt replied in a letter on 8 February 2021.

Correspondence between Health and Dr Anne Aly MP

Dr Aly wrote to Minister Hunt on 23 June 2021 asking that he consider meeting Mr s22 and another advocate, Mr s22 .

She stated that:

- Current CMIs do not have adequate warnings
- That the timeframe for existing CMIs to be updated into the new easier-to-use format was too long.
- That the issue could be resolved by simply adopting the lengthy warnings in FDA equivalents.

TGA has prepared a response to this correspondence.