Boxed Warning guidance

Public consultation paper

1. Required evidence to support a Boxed Warning

Q1: Do you support the proposal for evidence?

c) with modification

Q2: Do you envisage any difficulties with the proposed evidence requirements?

Evidence requirements for a boxed warning need to be flexible enough for the regulator to implement appropriate and warranted warnings early into the life cycle of a potentially problematic medication.

It takes an extended period of time for research into medication side effects to be published. There are constraints around funding and pharmaceutical companies don't appear to conduct research into side effects voluntarily. It is not in their financial interests to explore side effects, so without a mandated requirement for such research it may not be forthcoming.

Additionally, some scientists may not pursue research into medication side effects due to fear of litigation. An example of this occurred when a drug company, against the scientific findings of Neuroscientist Professor Doug Bremner, filed multiple lawsuits against him. This occurred in relation to his published research proving causation between the use of acne medication Roaccutane (Isotretinoin) and severe neuropsychiatric side effects (including suicide).

The two Montelukast advocacy groups, *Montelukast (Singulair) Side Effects Support and Discussion Group* and *Parents United for Pharmaceutical Accountability and Safety*, have been advocating in Australia, the USA and the UK, for increased warnings and safeguards around the use of Montelukast since 2008. Over the years medical professionals have dismissed the experiences of thousands of affected individuals, including multiple families that have lost loved ones to suicide. We are currently in the process of re-submitting a petition to the US FDA for a black box warning after it was originally rejected in the late 2000's. The body of published research is increasing however this has taken a significant period of time.

The considerable lag time between a medication being made available to the public and research into side effects being conducted is too great and can result in the suffering of many individuals.

The application process for consideration of a black box warning should be easily accessible to members of the public and consumer advocacy groups. Social media and the internet have created opportunities for affected individuals and/or their carers to connect and observe patterns of similar experiences. The medical community should adopt an increased respect for patients and their carers, as much can be learnt about common themes/struggles experienced by affected individuals.

Q3: What changes to the evidence requirements do you propose to address these difficulties, if any?

I recommend a broken lined box warning be established to identify where a medication

has strong indications of serious side effects, but has not yet acquired published research or sufficient evidence to meet requirements for a black box warning.

A broken lined box warning could act as a catalyst to encourage medical professionals to employ deeper level assessment of the user experience and to lodge Adverse Drug Reaction reports if concerns are identified.

Medical professionals and consumers should be provided with clear warnings about medications that have strong indications of severe neuropsychiatric side effects, especially when prescribed to children. A broken lined box warning would assist in these warnings being considered much earlier in the life span of the medication.

Safety standards of medications prescribed to children require more intense scrutiny, as children are unable to articulate, identify, communicate or understand side effects.

The culture surrounding Adverse Drug Reaction reporting needs improvement. Medical professionals should be obliged to lodge Adverse Drug Reaction Reports when patients or their carers report severe side effects.

Regulators need to improve methods of identifying severe side effects. Without the tireless campaigning of parents of Montelukast affected children, the safety concerns would not have been captured. We suggest regular 'big data' searches be conducted to pick up themes in social media posts/platforms to identify emerging safety issues of TGA approved medications as soon as they become detectible.

2. When a Boxed Warning is proposed

Q4: Do you support the proposed circumstances?

c) with modification

Q5: Do you envisage any difficulties with the circumstances under which a Boxed Warning is proposed?

Special consideration should be made to medications that are prescribed to children. Standards of safety should be increased due to a child's reliance on parents/carers to identify and act on their struggles and the communication barriers that exist in recognising side effects experienced by a child.

Q6: What circumstances should be removed, or should additional circumstances be included?

A Boxed Warning or as broken lined box warning should be proposed when a medication causes severe neuropsychiatric side effects such as suicidal ideation or suicide. This is particularly vital when prescribed to children, as they are unable to articulate, identify, communicate or understand side effects to the same degree as an adult.

Some medications may be safer for particular populations (eg. adults) than they are for other more vulnerable populations (eg. children or the elderly). Allowances should be made for Black Box or a broken lined box warning to be provided for certain population groups.

Prevention of mental health injuries should be a priority to Governments globally. We have a moral obligation to protect children from harm. Additionally it is fiscally irresponsible for Governments to allow the unsafe use of medications, and contribute to the creation of life-long mental illness in users.

As mental health is a priority for the Government of Australia, policy should be shaped to ensure that prevention is key in reducing mental health struggles within the community.

3. Content of the Boxed Warning in the PI

Q7: Do you support the proposal?

a) yes

c) with modification

Q8: What changes would you propose?

As an international advocate for the awareness of Montelukast side effects, I was startled to find that acknowledged side effects of medications vary from country to country. There appears to be a gap in global consultation on side effects. It is important that like-minded countries collaborate and share data not only on which medications have black box warnings but also on the side effects that are listed in the Product Information (PI) and (CMI) Medicines Information.

Pharmaceutical companies should be legally obligated to list side effects that have been acknowledged in other countries, at least the trusted Five Eyes countries - New Zealand, United States of America, United Kingdom and Canada.

It should be mandatory that medications that have a Black Box or a broken lined box warning include the CMI inside the product packaging. There should also be a compulsory warning on the outside of the packaging that states 'this medication has a black box safety warning'.

4. Boxed Warning and Consumer Medicine Information

Content and Format of the Boxed Warning in the CMI

Q9: Do you support the proposal?

a) yes

c) with modification

Q10: Are there other modifications or additions to the proposal you would like to make?

As described in previous responses I suggest a broken lined box warning to identify where a medication has strong indications of serious side effects, but has not yet

acquired published research or sufficient evidence to meet requirements for a black box warning.

A broken lined box warning should be linked to requirement of the medical community to report Adverse Drug Reactions to the Therapeutic Goods Administration.

5. Format of the Boxed Warning in the PI

Q11: Do you support the proposal?

a) yes

c) with modification

Q12: What changes would you propose?

The font size should be **larger** than the most common font size used in the PI.

Q13: Are there other modifications to the proposal you would like to make?

As described in previous responses I suggest a broken lined box warning to identify where a medication has strong indications of serious side effects, but has not yet acquired published research or sufficient evidence to meet requirements for a black box warning.

6. Changing or removing a Boxed Warning

Process requirements

Q14: Do you support the proposal?

c) with modification

Q15: Do you envisage any difficulties with the proposed process?

Communication processes between the TGA and stakeholders such as affected individuals, families and advocacy groups is lacking. Consumers need increased opportunities to be contributing to decisions about dangerous medications.

Attitudes towards affected individuals, their families and the advocacy groups we form are often dismissed by doctors and our experiences are rarely lodged officially to the TGA. Our collective experiences are valuable learning tools for the TGA and the medical community and greater interconnectivity between consumers and decision makers is vital.

Q16: Are there other modifications to the proposal you would like to make?

A formal application to change or remove a Black Box Warning or a broken lined box warning should be available to the sponsor, advocacy groups, members of the general public and medical professionals. Stakeholders should be given the opportunity to lodge their interest with the TGA in relation to specific medications or medication families.

When changes are requested by any of the parties previously mentioned, all stakeholders should be advised so they can provide input into the decision making process.

Greater opportunities should be available for consumers to make public testimony regarding their experiences and why they feel greater safeguards need to be adopted.

Consumers and the medical community should be able to access the literature reviews that are considered in decision making for each medication. The public and medical community should be able to log additional studies at any time for consideration in decision-making around the safety of a medication.

7. Promotional material

Two different options are being proposed for the inclusion of Boxed Warnings in promotional material, the proposal I support is:

Option 1

- All promotional material must include the Boxed Warning in full.

Promotional material

Q17: Which of the above options do you support?

a) Option 1

Option 1 is a safer option and will assist medical professionals and consumers in identifying the potential side effects of the medication. This will increase the knowledge required for ongoing monitoring of those using the medication. It will also be a reminder that Adverse Drug Reaction Reports are required for the medication.

Q18: Do you have any suggestions for how Boxed Warnings should appear or be referenced in promotional material (taking into account the different formats and media types which might be used to display this material)?

I am unsure of the circumstances in which medication sponsors can promote their products. I would recommend that products with a Black Box or a broken lined box warning be fully excluded from promoting to the general public. In the instance of a sponsor promoting to medical professionals, they should be obliged to list the warning in full and in prominent and large font.

8. Timelines and implementation

Q19: Do you support the proposal?

c) with modification

Q20: Do you envisage any difficulties with the proposed prospective implementation?

The quick and thorough implementation of a robust Black Box Warning system relies on the TGA to quickly capture relevant data on potentially dangerous medications. Policy should require sponsors to provide advice if their medications contain a Black Box Warning in any other country.

Q21: Are there other modifications or additions to the proposal you would like to make?

Black Box Warnings that exist in countries trusted by Australia should be automatically considered by the TGA for the equivalent warning in Australia. I refer in particular to our Five Eyes partners being the United Kingdom, the United States of America, Canada and New Zealand.

Medications that cause neuropsychiatric side effects that were listed in the TGA's recent medical alert (June 2018) should be automatically considered for a Black Box or a broken lined box warning.

- antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs)
- certain smoking cessation medications, including varenicline and buproprion (marketed as Champix and Zyban respectively)
- certain antiepileptics, including sodium valproate, carbamazepine, levetiracetam, phenytoin, lamotrigine, topiramate, pregabalin and gabapentin
- isotretinoin (marketed as Roaccutane)
- atomoxetine (marketed as Strattera and generic brands)
- montelukast (marketed as Singulair and generic brands)

Medications that already exist in the Australian pharmaceutical system should not be exempt from being considered for a Black Box Warning. Medications such as those listed above that have existing safety concerns should be automatically considered for a Black Box or a broken lined box warning.

Thank you for your consideration of this proposal.

Kindest regards,

Vanessa Sellick