Transparency Reforms and Evaluation Support Section
Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Dr Donna-Louise McGrath

[redacted]

16 August 2018

Consultation: Boxed Warning Guidance 2018

Dear TGA

I welcome the opportunity to respond to the Therapeutic Goods Administration consultation on the proposed requirements for Boxed Warnings on medicines. I have addressed the proposal based on my experience both as a carer for a rare disorder patient (Myasthenia Gravis), and as a social science researcher with an interest in health literacy and patient empowerment.

Regards

Dr Donna-Louise McGrath (*PhD)*

Consultation on Boxed Warning Guidance

Dr Donna-Louise McGrath (PhD)

I am responding to this consultation based on my experience as a carer for a rare disorder patient (Myasthenia Gravis) and as a social science researcher. Myasthenia Gravis (MG) is a comparatively rare neurological disorder which is characterised by 'a loss of the acetylcholine receptors that initiate muscle contraction; resulting in muscle weakness that can be life threatening' (Vincent 2002, p.1).

Medicines that interfere with neuromuscular transmission can be harmful to patients with Myasthenia Gravis (Olig & Fehrenbacher, 2017). However there appear to be no Boxed Warnings in Australia to alert MG patients, their carers, or their practitioners to the specific risks associated with those medicines.

Required evidence to support a Boxed Warning

While Boxed Warnings should generally be based on observed data from clinical and sometimes non-clinical sources, the voluntary reporting of adverse medicine related events is likely to result in under-reporting, particularly for MG patients.

- There is little awareness of adverse drug reaction reporting systems among Australian consumers (Robertson et al., 2013) and only 4% of adverse event data comes from general practitioners (Linger & Martin, 2018).
- There may be less reporting of adverse medicine events for the rare disorder Myasthenia Gravis (MG) patient because their adverse reaction to a medicine may be mistakenly attributed to a worsening of the MG condition itself. For example, fluoroquinolones may trigger a 'myasthenic crisis'.
- Sponsor reports of adverse events may lack important causal and correlative data (Linger & Martin, 2018).
- Clinical drug trials can exclude rare disorder patients; so that adverse effects may take longer to become apparent.

Given those limitations of national adverse event notification data, the following sources should also be considered as evidence to support a Boxed Warning for rare conditions such as Myasthenia Gravis (MG):

- Systematic reviews and case series reports (e.g. Jones et al., 2011).
- International post-market pharmacovigilance data (e.g. the FDA Adverse Event Reporting System, USA).
- International evidence for Boxed Warnings. For example, based on serious post-marketing adverse events, in 2011 the US Food and Drug Administration added a Black Box Warning to fluoroquinolones to warn of the risk of worsening symptoms for those with Myasthenia Gravis (see FDA 2016).

When a Boxed Warning on the Product Information (PI) is proposed

The circumstances in which a Boxed Warning is applied should include; avoiding or altering the use of a medicine in high risk populations in which a serious adverse reaction is identified. For example, medicines that interfere with neuromuscular transmission (e.g. fluoroquinolones) have been identified as harmful to patients with Myasthenia Gravis (e.g. Olig & Fehrenbacher, 2017; Sieb, 1998). A study of US FDA post-marketing adverse event reports found that fluoroquinolone exposure may result in potentially *life-threatening* Myasthenia Gravis exacerbations in patients with the underlying disorder (Jones et al., 2011).

A Boxed Warning on Product Information (PI) is a *risk mitigation measure*. In my experience as a carer for a Myasthenia Gravis (MG) patient, the absence of a Boxed Warning in Australia can result in fluoroquinolones being prescribed *as a first line of treatment* for uncomplicated infections; despite the fact that the PI states that the product ‘can lead to life-threatening weakness of the respiratory muscles in patients with Myasthenia Gravis’ (MG). Hence prescribers can overlook or *underestimate* that risk when they are unfamiliar with MG (being a rare disorder). That harm may be avoided if a Boxed Warning is added to both the PI and the CMI.

Boxed Warning and Consumer Medicine Information (CMI)

The Consumer Medicine Information (CMI) Boxed Warning and statement should be consistent with those in the Product Information (PI). Currently, the CMI and the PI for fluoroquinolones differ in Australia with regard to the disclosed risks to Myasthenia Gravis (MG) patients. While the PI informs the prescriber that the fluoroquinolone may "exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles", the CMI merely advises the consumer to "tell your doctor if you have Myasthenia Gravis" or experience worsening symptoms. However MG patients have a right to be fully informed of all medicine risks, particularly when effective safer alternatives are available and that those options could have been discussed with their pharmacist or practitioner in a shared-decision making model of health-care.

The PI and CMI Boxed Warnings and statements should be consistent. Patients and their carers should not be seen as passive consumers of medicines. They often search for information online when they have an adverse reaction to a medicine. For example, a worsening of Myasthenia Gravis (MG) has been reported following the use of timolol maleate eyedrops (e.g. Coppeto 1984; Shaivitz 1979; Verkijk 1985). The PI for several brands of timolol maleate eye drops discloses that MG risk, while the CMI makes no mention of MG.

A Boxed Warning on the CMI is an additional safety net if consumers such as the MG patient are prescribed a contraindicated medicine or their prescriber does not comply with a Boxed Warning. However anecdotal data also suggests that few Australians are receiving CMI with their prescription medicines (Aslani, 2007).

Format of Consumer Medicine Information (CMI)

I support the proposed format of the Boxed Warning, with some modifications:

- The Boxed Warning should be in a larger font size.
- Identified patient populations at risk could be underlined.

For example:

> **WARNING**: Fluoroquinolones can exacerbate muscle weakness in patients with Myasthenia Gravis and should be avoided. Serious adverse events…..

Timeline and implementation

I envisage difficulties with the proposition that Boxed Warnings will not be applied retrospectively unless new safety information becomes available. The voluntary reporting of adverse medicine related events results in under-reporting and there is a lack of awareness of adverse drug reaction reporting systems among Australian consumers (Robertson et al., 2013).

Further, there are roughly 24.1 cases of Myasthenia Gravis (MG) per one million persons in Australia[1] (Gattellari et al., 2012); so that statistically fewer adverse medicine related events will be reported for those patients, while others will go unreported when they are mistakenly attributed to a worsening of the MG condition itself. The required evidence to support a Boxed Warning should thus be inclusive of extant international data of adverse event reports and rigorously conducted systematic reviews and case series studies; particularly for rare disorder populations.

In addition, Boxed Warnings should be internationally consistent for the same medicines. For example, medicines such as fluoroquinolones interfere with neuromuscular transmission and have been identified as harmful to patients with Myasthenia Gravis (e.g. Olig & Fehrenbacher, 2017; Sieb, 1998). International post-market pharmacovigilance activities (e.g. the US FDA Adverse Event Reporting System) indicate safety concerns with fluoroquinolones and Myasthenia Gravis. In 2011 Black Box Warnings were thus added to fluoroquinolones in the USA to warn of those Myasthenia Gravis related risks (see FDA 2016). Australian Myasthenia Gravis patients are not less susceptible to those medicines and have a right to be informed of those risks.

[1] Based on 2009 prescriptions for Pyridostigmine Bromide.

References

Aslani, P. (2007). Consumer Medicine Information conundrums. *Australian Prescriber*, *30*(5), 122-4.

Coppeto, J. R. (1984). Timolol-associated Myasthenia Gravis. *American journal of ophthalmology*, 98(2), 244-245.

FDA. (2016). US Food and Drug Administration, FDA Drug Safety Communication: *Drug Safety Communications*, 26 July 2016. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM513019.pdf

Gattellari, M., Goumas, C., & Worthington, J. M. (2012). A national epidemiological study of myasthenia gravis in Australia. *European Journal of Neurology*, *19*(11), 1413-1420.

Jones, S. C., Sorbello, A., & Boucher, R. M. (2011). Fluoroquinolone-associated Myasthenia Gravis exacerbation. *Drug Safety*, *34*(10), 839-847.

Linger, M., & Martin, J. (2018). Pharmacovigilance and expedited drug approvals. *Australian Prescriber*, *41*(2), 50.

Olig, EJ & Fehrenbacher, L. (2017) 'Antibiotics that aggravate Myasthenia Gravis' Pharmacy Times, Dec 26 2017 https://www.pharmacytimes.com/publications/issue/2017/december2017/antibiotics-that-aggravate-myasthenia-gravis

Robertson, J., Newby, D. A., & Robertson, J. (2013). Low awareness of adverse drug reaction reporting systems: a consumer survey. *Medical Journal of Australia*, *199*(10), 684-6.

Shaivitz, S. A. (1979). Timolol and Myasthenia Gravis. *JAMA*, *242*(15), 1611-1612.

Sieb, J. P. (1998). Fluoroquinolone antibiotics block neuromuscular transmission. *Neurology*, *50*(3), 804-807.

Verkijk, A. (1985). Worsening of Myasthenia Gravis with timolol maleate eyedrops. *Annals of Neurology*, *17*(2), 211-212.

Vincent, A. (2002). Unravelling the pathogenesis of Myasthenia Gravis. *Nature Reviews Immunology*, *2*(10), 797.