Australian Government

Department of Health
Therapeutic Goods Administration

Ms Freda Villela
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The Coroners Court of Victoria
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TGA Reference: R14/1248568
Court Reference: 2010/4605

Dear Ms Villela,

Investigation into the death of PHOEBE HANDSJUK

I refer to your letter, dated 10 December 2014, advising the Therapeutic Goods Administration (TGA) of Coroner Peter White's inquest finding in relation to the death of Phoebe Handsjuk. You have requested a written response to the Coroner's recommendations which are documented on pages 87 and 88 of court document 2010/4605: *Inquest into the Death of: PHOEBE HANDSJUK*.

The Coroner's finding was that Phoebe Handsjuk, a 24 year old female with a history of mental health problems, died "on 2 December 2010 from exsanguination and injuries sustained while attempting to climb from a height, in the setting of alcohol and Stilnox consumption". The Coroner has recommended lowering the dosage of Stilnox in women and making only 5mg tablets available for supply in Australia.

Stilnox is a brand of the prescription medicine zolpidem, which is registered in Australia for the short term treatment of insomnia in adults and marketed under a number of brand names. Zolpidem is a sedative with properties similar to the benzodiazepines, such as diazepam. It was first registered in Australia in 1997 but was not marketed here until 2000. Zolpidem is indicated for short-term use only - up to a maximum of four weeks - under close medical supervision. It should not be used with alcohol and caution is advised if used with other central nervous system drugs.

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In 2006, safety concerns regarding zolpidem were identified by the TGA following reports of potentially serious changes in mental state and bizarre sleep behaviours, including driving while apparently asleep. The consumption of alcohol appeared to be a strong contributing factor in the risk of these adverse events. In response to these concerns, in 2008 the TGA placed a black box warning on the Product Information (PI) and Consumer Medicines Information (CMI) documents for all zolpidem products, including Stilnox. This is the highest level of warning used to alert people to the possible side effects of a medicine. The boxed warning advises that Zolpidem may be associated with potentially dangerous complex sleep-related behaviours, prohibits the co-consumption of alcohol, and limits use to a maximum of four weeks under close medical supervision. A warning was added to the front of the Stilnox package stating that it should not be taken with alcohol. The current PI and CMI documents for zolpidem products can be accessed via the TGA website at: https://www.ebs.tga.gov.au/

To assist in reducing the potential for prolonged use or misuse, the TGA has restricted the pack size for Zolpidem, which can only be supplied in packs of 14 tablets in Australia.

Coroner's first recommendation

The Coroner's first recommendation states:

> *"Specifically, I recommend to the ATGA, that in accord with current United States FDA requirements, that the dosage of Stilnox, recommended for administration to female patients be reduced by 50%, (which may be increased in accordance with individual patient requirements)."*

TGA response

The recommendation is under consideration by the TGA, and a decision is expected to be made by the end of 2015.

The Coroner's recommendation is being considered as part of an ongoing safety investigation by the TGA which is examining whether the currently available data support a reduction in the initial daily dose of zolpidem for women. Information related to the FDA's decision on zolpidem dosage and to the decision made by the European Medicines Agency (EMA), which differs from that of the FDA, is being considered.

In October 2013, the FDA recommended a reduction in the dose of zolpidem for women. The FDA's decision to lower the recommended starting dose to 5mg for women was made in relation to a specific safety concern, namely the risk of next-day impairment. It was not aimed at addressing the risk of abnormal sleep behaviours and it is not clear whether such sleep behaviours are dose-related or idiosyncratic[1]. Further information regarding the FDA's decision can be accessed via the FDA website at: http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm

[1] An idiosyncratic reaction is one that occurs rarely and unpredictably in patients and is not dose dependent.

The EMA, through its Pharmacovigilance Risk Assessment Committee (PRAC) also reviewed zolpidem. The PRAC recommendations were not to change the dosage but to make changes to the product information aimed at further minimising the known risks of next day impairment. The recommendations were endorsed by the European Commission and adopted by a European Union-wide legally binding decision on 23 June 2014. The PRAC *Assessment report for Zolpidem-containing medicinal products* is at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Zolpidem-containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500170687.pdf

Factors which contributed to the EMA's decision included a paucity of evidence of efficacy for the lower zolpidem dose, consideration of the risk of re-dosing if initial doses were ineffective and paucity of evidence that a reduced dose would significantly reduce the risk of impaired driving or somnambulism.

On 2 September 2014, the TGA approved changes the Australian Product Information (PI) for Stilnox to provide additional advice related to the dosing and safety of zolpidem, namely:

- Additional explanatory text was added to the dosing section to highlight that the treatment should be taken in a single intake, immediately at bedtime, and not be re-administered during the same night.
- A statement was added to the dosing section that "The lowest effective daily dose of zolpidem should be used and must not exceed 10 mg."
- Additional text was added in relation to "Next-day psychomotor impairment" and "Amnesia."
- Additional drug interactions statements were added.
- The text regarding driving and use of machinery was revised.
- The information regarding pharmacodynamics properties was revised.

The TGA communicated these changes in the Medicines Safety Update (MSU) published in the August 2014 Australian Prescriber, which is sent to medical practitioners and pharmacists by the National Prescribing Service (NPS), and on the TGA website. The MSU article is available via the TGA website at: https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-5-number-4-august-2014#zolpidem.

The TGA will provide the Victorian Coroner with an update in relation to the first recommendation once we have finished our evaluation of the relevant data.

Coroner's second recommendation:

The Coroner's second recommendation states:

> *"I further recommend that henceforward only 5 mg tablets, (rather than the 5 and 10 mg tablets currently in use), become the tablet size permitted to be supplied to all users in Australia. To elaborate, that one tablet size only, should be made available to both male and female patients, (and that a 10mg tablet, should not continue to be offered). Appropriate other reductions should continue to be mandated in respect of the elderly and the sick, all of which should be included in the manufacturer's product advice, together with other presently existing product information. This recommendation is made having particular regard to anecdotal evidence concerning the frequency of the shared use of sleeping tablet medication, and of the need to seek to reduce the possibility that such behaviour, undesirable as it is, will lead to an inadvertent overdose by either a female, or an elderly or ill recipient."*

TGA response

The Coroner's second recommendation is unable to be implemented by the TGA.

There are four dosage forms of Stilnox registered on the Australian Register of Therapeutic Goods (ARTG): Stilnox tablets 5mg; Stilnox tablets 10mg; Stilnox CR modified release tablets 6.25mg; and Stilnox CR modified release tablets 12.5mg. At the current time, however, the 5mg tablet is not marketed in Australia[2]. The 10mg tablets are scored to enable the tablet to be broken in half when a 5mg dose is required. Alternatively, the 6.25mg modified release tablet can be used in patients requiring a lower dose.

Currently, 10mg is the recommended dose for the majority of patients requiring zolpidem for the short term treatment of insomnia. Advice to the TGA from Sanofi, the Australian sponsor of Stilnox, is that marketing the 5mg dosage form in Australia is unlikely to be commercially feasible, given the availability of the scored 10mg dose and the lower dose modified release tablet.

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[2] The MSU article referred to above incorrectly indicates that the 5mg dosage form is currently marketed

As the TGA is not aware of any evidence that only supplying the 5mg dosage form would reduce the potential for misuse for this drug, the TGA has no regulatory basis to place a requirement on the sponsor to market a 5mg dose or to require that only a 5mg dose be marketed.

The contact information of the person responsible for consideration of the above recommendations is:

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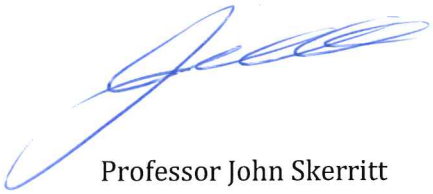
Yours sincerely,



Professor John Skerritt
National Manager
Therapeutic Goods Administration
4 March 2015