Australian Government

Department of Health

Deputy Secretary

Ms Genevieve James
Coroners Register
Coroners Court of Victoria
65 Kavanagh Street
Southbank Victoria 3006

Dear Ms James

Re: Investigation into the death of Sydney Kennedy

I refer to your letter, dated 10 February 2017, advising the Therapeutic Goods Administration (TGA) of Coroner Michelle Hodgson's finding without inquest in relation to the death of Sydney Hugh Kennedy and to my response of 30 March 2017.

As indicated in my letter of 30 March 2017 we have evaluated lithium toxicity in the Australian context. This evaluation included review of the current Product Information (PI) documents for lithium products and case reports of lithium toxicity in TGA's adverse event database.

From this investigation we conclude:

- lithium toxicity occurring within the target serum plasma concentration is a known risk
- the PI documents for lithium medicines (Lithicarb and Quilonum) provide prescribers with adequate advice about this risk and the information in the PI is aligned with current clinical practice guidelines.

We have responded to the Coroner's recommendation by publishing a Medicines Safety Update article on our website to remind health professionals to remain vigilant for signs of lithium toxicity, particularly in patients with risk factors. Please find attached the article that was published on 13 September 2017. Advice on toxicity and the appropriate monitoring of lithium levels was also directly provided to eleven colleges and associations with professional responsibility in this area of medicine.

Thank you for notifying the TGA of this matter.

Yours sincerely

Adj. Professor John Skerritt
Health Products Regulation Group

5 October 2017

Att - Medicines Safety Update Volume 8, 4 August-September 2017

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Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

Volume 8, Number 4, August-September 2017

In this issue

Lithium level monitoring and toxicity

Health professionals are reminded that early symptoms of lithium toxicity can occur close to or within the serum therapeutic range. You should remain vigilant for potential signs of lithium toxicity, particularly in patients with risk factors.

Lithium, marketed in Australia as Quilonum SR (450 mg sustained release tablets) and Lithicarb (250 mg tablets), is indicated for the treatment of acute mania, hypomania and for the prophylaxis of manic-depressive illness. Lithicarb is also indicated for the treatment of some cases of schizo-affective illness and character or personality disorders in young people with evidence of cyclothymia.

The risk of lithium toxicity is adequately addressed in the Product Information for Quilonum SR and Lithicarb, but a case heard in the Coroners Court of Victoria involving a patient who died in 2013 as a result of lithium toxicity has prompted this reminder. The patient was elderly and had a number of risk factors that increased the potential for this adverse reaction. A delay in attributing early symptoms of toxicity to lithium was also found to have contributed to the patient's death.

Narrow therapeutic index

There are relatively narrow margins between therapeutic and toxic dosages for lithium and therefore regular blood and clinical monitoring is important. In addition, toxicity occurring close to or within the target serum lithium concentration range is a known risk.

Failure to recognise the early signs of toxicity may lead to a delay in treatment and result in poor patient outcomes including, in the worst cases, death.

Symptoms and risk factors

Early symptoms of lithium toxicity are varied and non-specific. They are most likely to occur when serum lithium concentration exceeds 1.5 mmol/L but can occur when serum lithium levels are within the target concentration range. Symptoms/signs can include:

- fine hand tremor
- diarrhoea
- nausea/vomiting
- polyuria
- thirst
- drowsiness
- agitation
- ataxia and muscle weakness
- agitation
- hyperreflexia.

The most important site of toxicity is the central nervous system. Neurological manifestations of lithium intoxication such as ataxia, dysarthria, dysphagia and cognitive impairment may not be fully reversible despite appropriate treatment. Severe toxicity may result in convulsions, myoclonus and coma.

Lithium toxicity can result from a reduction in glomerular filtration, an increase in tubular reabsorption or altered volume of distribution. A

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TGA Health Safety Regulation

number of factors are known to increase the risk of toxicity including:

- impaired renal function
- advanced age (greater than 50 years)
- nephrogenic diabetes insipidus
- dehydration (including fluid loss from vomiting, diarrhoea and excess sweating)
- reduced salt intake
- thyroid dysfunction
- concurrent illness
- medicines that reduce lithium clearance (for example non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin 2 receptor antagonists and diuretics).

Additionally, the following factors are also associated with an increase in the risk of neurotoxicity:

- use of a controlled release formulation
- chronic supratherapeutic dosing.

Health professionals are reminded to be vigilant for the potential signs of lithium toxicity, particularly in patients with risk factors. Furthermore, it is recommended that health professionals educate patients and care providers regarding the early symptoms of lithium toxicity and counsel them to seek medical advice if any are suspected.

Adverse event reports

As of 17 May 2017, the TGA has received 58 reports in which lithium was suspected of causing toxicity. Two of these cases resulted in the death of the patient, including the one that was the subject of the aforementioned case heard by the Coroners Court of Victoria.

The serum lithium level was not reported in all cases describing toxicity. For the cases where it was provided, lithium levels ranged between 1.09 and 5.72 mmol/L. In seven cases the lithium level was less than 1.5 mmol/L.

Interactions with other medicines were identified as a contributing factor in 17 cases, and may have played a role in four other cases.

Inappropriate dosing was found to be a contributing cause of toxicity in two cases, and may have contributed to a third case.

New precautions for hyoscine butylbromide ampoules

Health professionals are reminded that parenteral administration of hyoscine butylbromide can cause tachycardia, hypotension and anaphylaxis and therefore it should be used with caution in patients with pre-existing cardiac conditions. Hyoscine butylbromide is marketed in Australia as Buscopan.

Hyoscine butylbromide is an antispasmodic. Its anticholinergic spasmolytic effect is based both on competitive inhibition of the parasympathetic activation of smooth muscle mediated through muscarinic receptors and, more markedly, through ganglionic blockade of neural transmission.

Hyoscine butylbromide ampoules, administered by intramuscular or slow intravenous injection, are used to treat spasm of the gastrointestinal tract, biliary spasm and renal spasm, and as a diagnostic aid in radiology.

The Australian Product Information (PI) for hyoscine butylbromide lists tachycardia, decreased blood pressure and anaphylaxis as potential adverse effects, but the PI is now being updated to include a stronger warning in the precautions section because these adverse events can be more serious in patients with cardiac conditions.

The updated PI will advise that hyoscine butylbromide ampoules should be used with caution in patients with pre-existing cardiac conditions, such as cardiac failure, coronary heart disease, cardiac arrhythmia or hypertension, and in cardiac surgery. Monitoring of these patients is advised and emergency equipment and personnel trained in its use must be readily available.

Australian adverse event reports

There are 28 cases describing tachycardia and/or hypotension relating to use of hyoscine butylbromide in the TGA's adverse events database. An additional four cases describe anaphylactic reactions. There is insufficient clinical information provided to determine whether or not these reactions occurred in people with pre-existing cardiac conditions. None of these cases reported death, cardiac arrest or myocardial infarction.