From the Lord O'Shaughnessy
Parliamentary Under Secretary of State for Health (Lords)

Department of Health

Department of Health
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Mr Martin Fleming
HM Senior Coroner, West Yorkshire (Western)
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13 SEP 2018

Dear Mr Fleming

Your reference: MDF-HK/1505-2017
Our reference: PFD 1143536

Thank you for your letter of 27 July to the Secretary of State for Health and Social Care about the death of Ms Kathleen Gabrielle Bamforth. I am responding as Minister with portfolio responsibility for medicines.

I was very saddened to read of the circumstances surrounding Ms Bamforth's death and have noted carefully the matters of concern raised in your report.

My officials have taken advice from the Medicines and Healthcare Products Regulatory Agency (MHRA) and the National Institute for Health and Care Excellence (NICE) on these matters.

On the matter of clinical guidelines, NICE has advised that its guidelines set out the expectation that prescribers will use a drug's Summary of Product Characteristics (SmPC), as well as the 'British National Formulary' (BNF) to inform decisions made with individual patients.

Regarding the prescribing of clomipramine, the NICE guideline, '*Depression in adults: recognition and management*' (CG90), includes recommendations on monitoring in relation to people taking tricyclic antidepressants (TCAs). The guideline is available at: https://www.nice.org.uk/guidance/cg90.

Recommendation 1.5.2.4 discusses the need for healthcare professionals to consider the specific cautions, contraindications and monitoring requirements for drugs (including TCAs), and recommendation 1.5.2.9 states that people who start on low-dose TCAs and who have a clear clinical response can be maintained on that dose with careful monitoring.

Where a patient has other health conditions or other medications they are taking, recommendation 1.5.2 states that healthcare professionals should discuss antidepressant treatment options with the patient, covering the choice of antidepressant, including any anticipated adverse events, such as side effects and discontinuation symptoms, and potential interactions with other medications they are taking for physical health problems.

This guideline is currently in the process of being updated by NICE and final recommendations have not yet been confirmed. Draft recommendations went out for second consultation earlier this year and are available from the NICE website at: https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0725/documents. The draft includes updated recommendations regarding monitoring (and evaluating) treatment adherences, and harms, with regard to pharmacological treatment. For example, recommendation 1.4.6 states:

'1.4.6 For interventions for people with depression:

- *review how well the treatment is working with the person*
- *monitor and evaluate treatment adherence*
- *monitor for harms of pharmacological and psychological treatment*
- *consider routinely using validated sessional outcome measures. [2018]'*

The draft recommendations may be subject to change following the consultation. I am advised that the expected publication date for the final guidance is yet to be confirmed.

I am also advised by the MHRA that clomipramine is known to be toxic in overdose, particularly in relation to its cardiovascular effects (hypotension, tachycardia, QTc prolongation and arrhythmia including Torsade de Pointes, conduction disorders, shock, heart failure; in very rare cases cardiac arrest); and neurological effects (somnolence, stupor, coma, ataxia, restlessness, agitation, hyperreflexia, muscle rigidity, choreoathetosis, convulsions, serotonin syndrome).

The SmPC for clomipramine includes warnings for prescribers about the possible risk of QTc prolongation and Torsade de Pointes, particularly at supra-therapeutic doses or supra-therapeutic plasma concentrations of clomipramine,

as well as warnings about the risks of serotonergic toxicity and convulsions. The SmPC also provides advice on drug interactions and other conditions which may increase the risk of toxicity with clomipramine and advises measures to take to reduce the risk of toxicity, including adherence to the recommended doses of clomipramine and not exceeding the recommended daily dose.

In relation to the additional prescribed medication detailed in your report, the clomipramine SmPC advises that concurrent use of clomipramine with drugs that are substrates or inhibitors of cytochrome P450 2D6 is not recommended as these drugs may increase the plasma concentration of clomipramine; opiates (such as tramadol) are included in the list of examples of such drugs provided in the SmPC. The SmPC for tramadol advises that tramadol can increase the potential for TCAs to cause convulsions, and that concomitant use of tramadol and TCAs may cause serotonin syndrome. Clomipramine is not recognised to interact with the other prescribed medication in your report (pregabalin and naproxen).

With regard to the long-term use of clomipramine, the SmPC recommends monitoring cardiac and hepatic function during long-term therapy. Routine blood screens to check clomipramine levels in these patients are not currently recommended.

The SmPC and Patient Leaflet for clomipramine and tramadol are available in full on the MHRA website at: http://www.mhra.gov.uk/spc-pil/.

The MHRA has confirmed that it is seeking advice from its independent experts, who advise the Commission on Human Medicines, on the merits of routine blood screens during long term use of clomipramine.

The MHRA aim to provide an update in October 2018. To assist with consideration of this issue, it would be helpful to the MHRA if you could provide a full redacted copy of your report into this case. This can be directed to Jose Miyar, Vigilance and Risk Management of Medicines Division, MHRA, 10 South Colonnade, Canary Wharfe, London E14 4PU.

Please note that the MHRA has added this case to its adverse drug reaction database under the Yellow Card reference number ADR 24338113.

17 SEP 2018

I hope this information is helpful. Thank you for bringing your concerns to our attention.

JAMES O'SHAUGHNESSY