The Rt Hon Dame Andrea Leadsom DBE MP
Parliamentary Under Secretary of State for Public Health, Start for Life and Primary Care
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Department of Health & Social Care

[redacted]

Mr Stephen Simblet KC
Assistant Coroner for the Area of Essex
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[redacted]

13 May 2024

Dear Mr Simblet KC,

Thank you for the Regulation 28 report to prevent future deaths of 29 September 2023 about the death of Mr Frederick William Le Grice**.** I am replying as Minister with responsibility for prescribing.

Firstly, I would like to say how saddened I was to read of the circumstances of Mr Le Grice's death and I offer my sincere condolences to his family and loved ones. The circumstances your report describes are concerning and I am grateful to you for bringing these matters to my attention. Please accept my sincere apologies for the significant delay

The report raises the following concerns:

- There is a known, albeit rare side effect of Nitrofurantoin, of it causing lung damage. Nevertheless, neither the deceased himself, nor the clinicians involved in the deceased's urinary care, who due to its specialism also have a prescribing function, were aware of the risk of lung damage from Nitrofurantoin:
- It is not very clear in the guidance to general practitioners or patients generally, that the patient and the treating clinicians should be particularly alert to any signs of coughing or breathlessness, and that if they are present, it may well suggest that Nitrofurantoin is causing damage to the patient's lungs. Such damage is likely to be irreversible.
- Concerns as to the effectiveness of the guidance and information available: (i) to general practitioners and prescribers treating those using urinary catheters

and/ or suffering from urinary tract infections; (ii) clinical staff in urology care; (iii) patients themselves Of the danger that Nitrofurantoin might cause lung damage, and (a) the need for all to be particularly vigilant as to symptoms and signs such as coughing or difficulty in breathing, and the desirability of their breathing and respiratory abilities being regularly monitored when a patient is using Nitrofurantoin (b) produces leaflets/ information resources to that effect.

In preparing this response, Departmental officials have made enquiries with Medicines and Healthcare products Regulatory Agency (MHRA). I am also aware that you have received a full and comprehensive response from NHS England who have worked closely with the MHRA on some of the key concerns.

The MHRA is an Executive Agency of the Department of Health and Social Care (DHSC) with responsibility for the regulation of medicinal products in the UK. The MHRA ensures that medicines are efficacious and acceptably safe, and that any possible side effects which have been recognised to occur with use of a medicine are appropriately described in the authorised product information. This comprises the Summary of Product Characteristics (SmPC, intended for healthcare professionals), labelling, and Patient Information Leaflet (PIL, provided to patients in each medicine pack). The MHRA does not regulate any additional sources of advice healthcare professionals may use when prescribing medicines, such as NICE (National Institute for Health and Care Excellence) guidelines or any local guidance.

As you have said, you undertook Mr Le Grice's inquest in 2022; in early 2023, the MHRA conducted a review of the available evidence concerning nitrofurantoin and pulmonary adverse drug reactions. The review considered the known safety profile of nitrofurantoin and the information on pulmonary adverse reactions already reflected in the product information. This followed a Regulation 28 Report to Prevent Future Deaths (https://www.judiciary.uk/wp-content/uploads/2022/03/Jane-Allison-Prevention-of-future-deaths-report-2022-0071_Published.pdf).

The conclusion of this review was that the potential for pulmonary Adverse Drug Reactions (ADRs) in patients taking nitrofurantoin is well established by the available data, including published scientific literature and a small number of reports of nitrofurantoin and fatal respiratory failure received by the MHRA. Information about these ADRs was present in the product information for nitrofurantoin for healthcare professionals and patients prior to this MHRA review. However, the review concluded that the product information should be further updated, to strengthen information on the need to be vigilant for respiratory symptoms, and to ensure that these warnings are sufficiently prominent.

As part of the review the MHRA received independent expert advice from the Commission on Human Medicine's Pharmacovigilance Expert Advisory Group (PEAG), who supported the recommendation that safety information should be updated to raise awareness amongst healthcare professionals and patients of the need to be vigilant for any new breathing symptoms when taking nitrofurantoin.

Marketing Authorisation Holders (MAHs) of nitrofurantoin were informed of the outcome of the review and were asked to make changes to the existing warnings in the product information:

For healthcare professionals (SmPC):

- to add details about the signs of pulmonary damage (as part of the existing warning that nitrofurantoin should be discontinued if these reactions occur);
- to highlight that these ADRs may occur with either short-term or long-term treatment;
- to advise that healthcare professionals should be vigilant for respiratory symptoms in patients who have just started treatment with nitrofurantoin (alongside existing advice that patients receiving long-term treatment should be closely monitored).

For patients (PIL):

- to expand the existing warnings about pulmonary ADRs, making these more prominent;
- to highlight that these ADRs may occur with either short-term or long-term treatment;
- to advise patients to talk to their doctor if they experience symptoms that may be caused by pulmonary ADRs.

To raise further awareness amongst healthcare professionals to be alert to the risks of pulmonary ADRs, and to advise healthcare professionals that they should tell patients and caregivers to be vigilant for new or worsening respiratory symptoms while taking nitrofurantoin, the MHRA published a Drug Safety Update (DSU) bulletin in April 2023: https://www.gov.uk/drug-safety-update/nitrofurantoin-reminder-of-the-risks-of-pulmonary-and-hepatic-adverse-drug-reactions. DSU is a monthly publication which MHRA uses to communicate important medicines safety information to UK healthcare professionals.

The MHRA will continue to keep the issue of nitrofurantoin and pulmonary ADRs under close review.

I hope this response is helpful. Thank you for bringing these concerns to my attention.

Best wishes,

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THE RT HON DAME ANDREA LEADSOM DBE MP