Medicines & Healthcare products
Regulatory Agency

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18 July 2022

Dear Mr Oliver,

Regulation 28 Report concerning Jane Elizabeth Allison (nitrofurantoin)

Thank you for your email dated 14th April 2022, in which you asked the Medicines and Healthcare products Regulatory Agency (MHRA) to provide a response to the Regulation 28 Report to Prevent Future Deaths following the inquest into the sad death of Ms Jane Elizabeth Allison.

Your report identified a number of matters of concern, including the following points relating to information available for healthcare professionals about the potential pulmonary side effects of nitrofurantoin:

1. **The patient died of acute pulmonary damage following the administration of nitrofurantoin for a urinary tract infection (course of treatment 10 days), however the BNF does not advise healthcare professionals to be alert to the danger of sudden pulmonary deterioration in elderly patients.**

2. **The BNF is deficient in providing advice as to monitoring and being alert for acute pulmonary damage. If the patient or her GP had been aware of this possible side effect, they might have been able to intervene earlier to avoid her death.**

3. **The information sent out with nitrofurantoin should be reviewed.**

The MHRA is the 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).

As you have noted, the product information for nitrofurantoin does list pulmonary and respiratory issues as possible side effects. We have conducted a review of the available evidence concerning nitrofurantoin and pulmonary adverse drug reactions and sought expert advice from the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines on the

strength of the evidence and whether the nitrofurantoin product information should be further amended.

As you will be aware, nitrofurantoin has been widely used in the UK since the 1950s for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. Aside from Ms Allison's case, as of 10th May 2022, we have received a small number of other fatal Yellow Card reports of nitrofurantoin and respiratory failure, with other durations of use. Some of these cases offer possible alternative explanations for the events, either due to the patient's previous medical history or concomitant medications that are themselves associated with respiratory reactions.

The PEAG agreed that pulmonary adverse reactions in patients taking nitrofurantoin are generally well known and that the frequency of these events appears low. Furthermore, there are no significant new data on the risk considering the cumulative exposure to this drug in the UK which is likely to be in the order of millions of people. It was agreed that awareness amongst healthcare professionals and patients should be improved so they are alert for any new breathing symptoms when taking nitrofurantoin.

Action being taken by the MHRA

In summary, we have considered the available evidence on nitrofurantoin and acute pulmonary reactions and, based on expert advice from the PEAG, will request that Marketing Authorisation Holders (MAHs) strengthen the wording in the UK Summary of Product Information (SmPC) and Patient Information Leaflet (PIL).

We are aware that the BNF, which is not the responsibility of the MHRA, has recently updated the nitrofurantoin monograph. These updates, adding additional information on acute pulmonary reactions, are in line with the current UK SmPC and PIL. The MHRA will communicate any SmPC and PIL updates, to the BNF, so that they can further revise their monograph as needed.

Companies marketing nitrofurantoin will be requested to emphasise to healthcare professionals and patients/carers in the nitrofurantoin product information the need to be vigilant for respiratory symptoms including during use to treat acute urinary tract infections, and to ensure that these warnings are sufficiently prominent.

The PEAG also agreed that it would be appropriate to communicate to UK healthcare professionals to inform them of these updates and remind them of the potential for pulmonary and chronic adverse drug reactions in association with nitrofurantoin, and that any such symptoms should be investigated and reported promptly. The PEAG considered that an article in the MHRA's monthly 'Drug Safety Update' bulletin may be an appropriate method to communicate these messages, and we will be taking this forward.

We will continue to keep the issue of nitrofurantoin and acute pulmonary reactions under close review, and we will let you know when the product information updates are complete and the Drug Safety Update Bulletin has been issued.

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Yours sincerely

[redacted]

[redacted]
Chief Executive
Medicines and Healthcare products Regulatory Agency