Department of Health & Social Care

From Nadine Dorries MP
Minister of State for Patient Safety, Suicide Prevention and Mental Health

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Your Reference: [redacted]
Our Reference: [redacted]

Ms Louise Hunt
HM Senior Coroner, Birmingham and Solihull
HM Coroner's Court
50 Newton Street
Birmingham B4 6NE

17th November 2020

Dear Ms. Hunt,

Thank you for your letter of 17 August to Matt Hancock about the death of Mr Ian Allen. I am responding as Minister with responsibility for mental health services and I am grateful for the additional time in which to do so.

First, I would like to say how saddened I was to read of the circumstances of Mr Allen's death and I extend my condolences to Mr Allen's family and loved ones at this difficult time. We must do all we can to learn from Mr Allen's death to avoid such tragedies from occurring again.

In preparing this response, my officials have taken advice from NHS England and NHS Improvement (NHSEI), the National Institute for Health and Care Excellence (NICE) and the Medicines and Healthcare products Regulatory Agency (MHRA).

As you may be aware, the MHRA is responsible for the safety of medicines and medical devices. The MHRA seeks independent expert advice from the Commission on Human Medicines (CHM) which advises on whether the overall balance of benefits and risks of medicines is favourable at the time of licensing and remains so thereafter.

The MHRA advises that detailed guidance regarding the monitoring requirements for clozapine is provided in the authorised product information which consists of the Summary of Product Characteristics (SmPC) for prescribers and the Patient Information Leaflet (PIL) which is supplied with each pack of medicine. The SPC and the PIL for licensed medicines (including clozapine) can be downloaded from the MHRA website[1].

[1] https://www.gov.uk/guidance/find-product-information-about-medicines

The patient monitoring requirements for clozapine include the measurement of clinical parameters such as regular full blood counts; blood pressure; electrocardiograms; hepatic enzymes; blood sugar; lipids and weight. Therapeutic drug monitoring of blood plasma levels is not currently required under the terms of the clozapine marketing authorisation.

I am informed by the MHRA that following the issue of two previous Prevention of Future Deaths reports that raised concerns about the need for monitoring of clozapine blood levels, and monitoring antipsychotic blood levels during long-term high-dose antipsychotic use, Expert Advisory Groups (EAGs) of the CHM considered safety data for clozapine and other antipsychotic drugs.

The EAGs advised that blood concentrations of clozapine should be monitored for toxicity in certain clinical situations. For example, when a patient stops smoking or switches to an e-cigarette, concomitant medicines may interact to increase blood clozapine levels; when a patient has pneumonia or other serious infection; and when poor (reduced) clozapine metabolism is suspected, or toxicity is suspected. I can confirm that the UK product information for clozapine has now been updated to include this advice on monitoring blood clozapine levels for toxicity. If blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis[2].

The EAGs also advised that, where assays (a laboratory investigative procedure) and suggested reference values are available, blood level monitoring of other antipsychotic drugs may be helpful in certain circumstances.

Following the outcome of these reviews, the MHRA communicated advice on monitoring blood concentrations of clozapine and other antipsychotics in the August 2020 edition of Drug Safety Update[3], which is the MHRA's monthly newsletter for healthcare professionals about medicines safety. The MHRA worked with the Royal College of Psychiatry and authors of the Maudsley Prescribing Guidelines on the recommendations to healthcare professionals in this article.

The DSU article focuses on drug blood level monitoring for toxicity of clozapine and other antipsychotics. It is recognised that blood level monitoring of these medicines can be beneficial in the care and management of patients, particularly those with treatment-resistant conditions[4]. For example, monitoring of blood clozapine levels may be useful when a patient starts (or re-starts) smoking as this may lead to a decrease in blood clozapine levels and dose adjustment may be necessary. The PIL for clozapine advises patients to tell their doctor if they smoke and that sudden changes in the patient's smoking habits can change the effects of clozapine. The MHRA communicated advice on smoking and smoking cessation and clinically significant interactions with commonly used medicines, including clozapine, in October 2009[5].

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[2] A condition that causes a low white blood cell count.

[3] https://www.gov.uk/drug-safety-update/clozapine-and-other-antipsychotics-monitoring-blood-concentrations-for-toxicity

[4] Maudsley Prescribing Guidelines. 13th edition. May 2018

[5] https://www.gov.uk/drug-safety-update/smoking-and-smoking-cessation-clinically-significant-interactions-with-commonly-used-medicines

One of the ways in which the MHRA monitors the safety of licensed medications is through the Yellow Card Scheme which receives information from both healthcare professionals and patients on side effects suspected to be associated with medicines. The concerns in your report have been added to the MHRA's adverse drug reaction (ADR) database under Yellow Card reference number ADR 24519396.

Prescribers are expected to follow national medicine guidance as well as the SmPC when making prescribing decisions. In 2019, NICE conducted a surveillance review of Clinical Guideline 178 *Psychosis and schizophrenia in adults: prevention and management* in which it considered, among other matters, the concerns highlighted in a previous Prevention of Future Deaths report in relation to clozapine monitoring[6].

NICE advises that while it is recognised that the current recommendations in the NICE guideline may not fully take account of the adverse effects and risks of toxicity associated with the use of clozapine, these are specified in detail in the British National Formulary[7] and, as already explained, the SmPC for prescribers which contains advice on interactions that can influence blood levels of clozapine.

The topic experts conducting the surveillance review recommended an update to NICE clinical guideline 178 was not required. The considerations and the outcome of the NICE surveillance review are published on the NICE website[8]. NICE has advised that the concerns in your report have been logged against clinical guideline 178, to be revisited when the guideline is next considered for review.

I am further advised that NICE has liaised with the publishers of the BNF (the British Medical Association and the Royal Pharmaceutical Society) regarding the appropriateness of updating the BNF information on clozapine to highlight the MHRA's recent Drug Safety Update. This change is now reflected in the BNF[9].

In addition, you may wish to note that NHSEI will ensure that all guidance relevant to clozapine prescribing and the risks associated with toxicity are shared with primary and acute NHS care through its established networks.

In relation to the local response to your report, I am advised that the Birmingham and Solihull Mental Health NHS Foundation Trust has responded to your report to explain that it has undertaken a review and update of its guidance on the use of clozapine to reflect the MHRA update in August 2020. I am further advised that the Trust has taken additional

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[6] https://www.judiciary.uk/publications/thomas-jackson-2/

[7] A UK pharmaceutical reference book provided to eligible prescribers working in the NHS and other organisations that provide NHS-commissioned care in England

[8] https://www.nice.org.uk/guidance/cg178/resources/2019-exceptional-surveillance-of-psychosis-and-schizophrenia-in-adults-prevention-and-management-nice-cg178-6718794445/chapter/Surveillance-decision?tab=evidence

[9] https://bnf.nice.org.uk/drug/clozapine.html#importantSafetyInformations

measures, such as additional training and education for pharmacists and post-graduate medical practitioners on clozapine; an audit of patients currently prescribed clozapine; and to include clozapine in a strengthened focus on physical health at multi-disciplinary meetings. I welcome the action taken by the Trust and encourage the Trust to continue to take forward the learning from Mr Allen's death.

Finally, I note that you copied your report to national oversight organisations, NHSEI and the Care Quality Commission. My officials have also brought your report to the attention of the Healthcare Safety Investigation Branch (HSIB) to support its intelligence monitoring of patient safety risks in relation to NHS-funded care in England. HSIB is the body responsible for conducting independent investigations of serious patient safety incidents in NHS-funded care across England, with a specific focus on system-wide learning and improvement. HSIB decides what to investigate based on intelligence from a number of sources about patient safety risks, and according to set criteria.

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

NADINE DORRIES