Medicines & Healthcare products
Regulatory Agency

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom
**gov.uk/mhra**

Mrs Louise Hunt
Senior Coroner for Birmingham and Solihull
50 Newton Street
Birmingham
B4 6NE

6th October 2023

Dear Mrs Hunt,

**Regulation 28 Report concerning Mohammed Khalid Hussain**

Thank you for your report dated 12th July 2023, in which you asked the Secretary of State for Health to provide a response to the Regulation 28 Report to Prevent Future Deaths following the inquest into the sad death of Mr Mohammed Khalid Hussain. Your request has been passed to the Medicines and Healthcare products Regulatory Agency (MHRA) as we are the regulator of medicines, medical devices and blood components for transfusion in the UK. We would like to extend our sincere sympathies to the family of Mr Hussain for their loss.

Your report identified a number of matters of concern, including the following points relating to clozapine:

1. There is no clear system for monitoring actual clozapine or clozapine levels and there is no safe system to communicate high levels of clozapine;

2. In this case, the patient's consultant indicated that clozapine should be reduced on the next prescription, and this was communicated by email, but this was not read or acted upon. You note that the inquest heard there was no safe system to effect medication changes;

3. That clozapine and norclozapine levels are recorded in the pharmacy section of the records but there was no system in place for highlighting high clozapine levels;

4. That there was a lack of understanding of when to measure clozapine levels, how to interpret high clozapine levels and how to respond to these;

5. You note that a Regulation 28 report was sent in August 2020 which identified that there was no system in place to ensure abnormal clozapine levels were escalated and acted upon and there was a lack of understanding of the importance and frequency of clozapine monitoring;

6. You raise concerns about the quality of the internal investigation process and whether it can identify central issues in a particular case;

7. That the processes within the pharmacy were not effective due to a lack of resources.

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 SmPC is a source of advice for healthcare professionals (HCPs) on the safe and effective use of a medicinal product.

We have considered the evidence provided and the circumstances leading to Mr Hussain's death. It is noted that he was established on clozapine in 2004 and in October 2022 a decision was made to reduce his medication, but this did not occur. As you note, there is a well-established system in place for monthly monitoring of white blood cell count in patients who are receiving clozapine.

The MHRA has previously been alerted to a fatal case involving clozapine toxicity. This issue was reviewed and considered by our expert advisory committee. In August 2020, the MHRA issued a Drug Safety Update article advising monitoring of blood concentrations of clozapine for toxicity in certain clinical situations (Clozapine and other antipsychotics: monitoring blood concentrations for toxicity - GOV.UK (www.gov.uk). These include when: a patient stops smoking or switches to an e-cigarette; concomitant medicines are prescribed which may interact to increase blood clozapine levels; a patient has pneumonia or other serious infection; reduced clozapine metabolism is suspected, or toxicity is suspected. The advice of the MHRA and the Commission on Human Medicines is that clozapine blood concentration monitoring should be carried out in addition to the required blood tests to manage the risk of agranulocytosis.

It is important to note that the terms of the SmPC do not impose drug level monitoring and this is an optional measurement. Any monitoring of clozapine plasma levels is done on an individual basis due to inter-patient variability and the SmPC does not define safe upper limits. The SmPC highlights certain clinical situations when blood clozapine level monitoring is advised as outlined above. Clozapine is well known to be associated with cardiac toxicity and the SmPC lists extensive information regarding this, including cases of fatal myocarditis and myocardial infarction.

Unfortunately, it is not within our remit to comment on the clinical care in specific cases. Similarly, we are not able to comment on the quality of the internal investigation process or pharmacy resourcing. We will continue to keep the issue of monitoring for clozapine toxicity

under close review, including reviewing Yellow Card cases and we will be writing to the marketing authorisation holders to investigate further thresholds for clozapine toxicity.

Yours sincerely,

[redacted]
Chief Safety Officer
Medicines and Healthcare products Regulatory Agency