Medicines & Healthcare products
Regulatory Agency

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Mr Andrew Harris
Assistant Coroner
London South Jurisdiction
By Email: [redacted]

Reference: [redacted]

10 March 2025

Dear Mr Harris,

Regulation 28 Report relating to the death of Luke Alexander Worrell

Thank you for your Regulation 28 report relating to the death of Mr Luke Alexander Worrell which was received on 20th February 2025. I would like to offer my sincere condolences to Mr Worrell's family on their tragic loss.

I understand from your report that Mr Worrell's death resulted from ruptured oesophagus, vomiting from ileus and gastro-intestinal upset associated with clozapine treatment. Your report identified the following matters of concern relating to clozapine:

1. There was lack of awareness by a series of clinical staff of the potential fatal side effects of clozapine.

2. There was an inappropriate use of community treatment order, when there was sufficient evidence to keep the patient on a Mental Health Act section.

The Medicines and Healthcare products Regulatory Agency (MHRA) is an executive agency of the Department of Health and Social Care with responsibility for the regulation of medicinal products in the UK. We ensure that medicines are efficacious and acceptably safe, and that information to aid the safe use of a medicine, including possible side effects 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 product information can support discussions between healthcare professionals and patients. The PIL is not intended to replace the discussion with prescribers about the benefits and risks of treatments.

The current special warnings and precautions for use section of the SmPC for clozapine states within the sub-section relating to anticholinergic effects that,

> "Clozaril has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction ischaemia (see section 4.8). On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated."

Gastrointestinal disorders are also described in the undesirable effects section of the SmPC of clozapine, which lists constipation, intestinal obstruction and paralytic ileus as possible adverse reactions to the treatment with clozapine. In addition, the contraindication section states that clozapine is contraindicated in patients with paralytic ileus. Similar messages can be found in the current PIL for clozapine.

In October 2017, we published an article in our bulletin Drug Safety Update which was distributed to healthcare professionals reminding of the potential fatal risks of intestinal obstruction, faecal impaction, and paralytic ileus. This information is also highlighted in the British National Formulary.

We have considered the evidence provided and the circumstances leading to Mr Worrell's death and acknowledge that your concerns relate to lack of awareness of clinical staff of the potentially fatal side effects of clozapine, and clinical decisions. Unfortunately, we cannot directly address these points, as it is not within our remit to comment on the clinical decisions in specific cases.

We continuously review the safety of medicines on the UK market and take appropriate regulatory action as required. Currently, we are reviewing the product information for clozapine. As part of this review, we will be giving careful consideration to the information which is provided to healthcare professionals, patients and their families and carers, and whether this can be improved to provide greater clarity. We intend to engage with relevant stakeholders during this process to ensure the regulatory documents meet the needs of patients and prescribers. It is anticipated that this review of clozapine will be completed this year, and we will inform you of the outcome.

Should you have any further questions, please do not hesitate to contact my office at Executive.Office@mhra.gov.uk.

Yours sincerely

[redacted]
[redacted]
Chief Executive
Medicines and Healthcare products Regulatory Agency
E: [redacted]