Medicines & Healthcare products
Regulatory Agency

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

Ms Louise Wiltshire
Assistant Coroner for County of Devon, Plymouth and Torbay
By Email: [redacted]

Reference: [redacted]

19 March 2025

Dear Ms Wiltshire,

Regulation 28 Report into the death of William Antony Northcott

Thank you for your Regulation 28 Report relating to the death of William Antony Northcott. I would like to offer my sincere condolences to Mr Northcott's family on their tragic loss.

I understand from your report that Mr Northcott's death resulted from sudden cardiac arrhythmia caused by the combined effect of mixed drug toxicity with a background of an enlarged heart and left ventricular hypertrophy. Mr Northcott's medication included clozapine and fluoxetine which were prescribed and maintained at therapeutic levels. Postmortem toxicological analysis also revealed amphetamine levels consistent with recreational use.

Clozapine, fluoxetine and amphetamine are all recognised to be cardiotoxic drugs and carry risk of causing sudden cardiac arrhythmia. Your report identified the following matters of concern relating to clozapine and fluoxetine.

1. That the discussion and repetition of information surrounding red flags and side effects associated with clozapine, and advice about when to seek medical attention, will be significantly more limited for those patients attending their GP practice than for those attending the monthly clozapine clinics under the care of Devon Partnership Trust, and that this may be a national issue.

2. That clozapine-related cardiomyopathies could go undetected in patients under the care of Devon Partnership NHS Trust who are prescribed clozapine and leave them at unknown increased risk of fatal cardiac arrythmias, and that this may be a national issue.

3. That communication from healthcare professionals at Devon Partnership NHS Trust of important issues to patients suffering from treatment resistant schizophrenia was not as clear as it should have been.

The Medicines and Healthcare products Regulatory Agency (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 information to aid the safe use of a medicine, including possible side effects are appropriately described in the authorised product information.

This information 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 cardiovascular disorders:

> "Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal. Pericarditis/pericardial effusion and cardiomyopathy have also been reported in association with clozapine use; these reports also include fatalities."
>
> "If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist."

Cardiac disorders are also described in the 'undesirable effects' section of the SmPC of clozapine, which lists arrhythmias, cardiac arrest and cardiomyopathy as possible adverse reactions to the treatment with clozapine. In addition, the contraindication section states that clozapine is contraindicated in patients with "severe renal or cardiac disorders (e.g. myocarditis)". The section on interaction with other medicinal products states that "Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, sertraline, are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely." Similar messages can be found in the current PIL for clozapine.

We have considered the evidence provided and the circumstances leading to Mr Northcott's death and acknowledge that most of your concerns relate to clinical discussions between a patient and their prescriber or via the clinical care delivered by the Trust. Unfortunately, the MHRA cannot directly address these points, as it is not within our remit to comment on the clinical care in specific cases.

The MHRA continuously reviews the safety of medicines on the UK market and take appropriate regulatory action as required. Currently, the MHRA is 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.

Should you have any further questions, please do not hesitate to contact my office: [redacted]

Yours sincerely,

[redacted]

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