Medicines & Healthcare products
Regulatory Agency

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

Mr Crispin Oliver
Senior Assistant Coroner for County Durham and Darlington

[redacted]

9th April 2024

Dear Mr Oliver,

Regulation 28 Report concerning Sean Benjamin Crawford

Thank you for a copy of your report dated 15th February 2024, 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 Mr Sean Benjamin Crawford. We would like to extend our sincere sympathies to the family of Mr Crawford for their loss.

I understand from your report that Mr Crawford's death resulted from the combined toxic effect of alcohol and clozapine, which were individually not at toxic levels, but acted together to suppress his central nervous system. Your report identified the following matters of concern relating to clozapine:

1. There is no guidance in any academic literature, the British National Formulary, or NICE or MHRA advice on the dangers of death when comparatively high, but not fatal, levels of both clozapine and ethanol in the blood result in central nervous system depression.

2. The patient information leaflet and wording on the outer label do not advise of the risk of death when clozapine and alcohol are taken together.

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.

Information regarding interactions is included in section 4.5 of the SmPC for every medicinal product. The current interactions section of the SmPC for clozapine states within the sub-section relating to contraindications of concomitant use that, “alcohol should not be used concomitantly with clozapine due to possible potentiation of sedation.” This section also includes a table noting the enhanced central effects of alcohol and that additive CNS depression and cognitive and motor performance interference may occur when it is used in combination with clozapine. This section also states that patients should be advised of the possible additive sedative effects and that they should be cautioned not to drive or operate machinery. As you have noted, the current PIL for clozapine includes the statement, “do not drink alcohol during treatment with clozapine.” Furthermore, when clozapine is dispensed it must also have a cautionary label which includes the warning “do not drink alcohol”. However, none of these materials specifically mention any risk of death because of the interaction with alcohol.

We have considered the evidence provided and the circumstances leading to Mr Crawford’s death. We have also recently met with a member of Mr Crawford’s immediate family to discuss their concerns. Some of these relate to clinical discussions between a patient and their prescriber which we are not able to address, as it is not within our remit to comment on the clinical care in specific cases. However, because of the nature of some of the concerns raised, we intend to conduct a further assessment of the information provided within the clozapine product information regarding drug-drug interactions. As part of this assessment, 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. We intend to engage with relevant stakeholders during this process to ensure that their concerns are addressed. This assessment will be considered as part of a wider review of clozapine which will be completed this year.

We are aware that you have also written to the BNF, and we will work with them as our assessment progresses. In the meantime, we will continue to closely monitor the safety of clozapine, including cases of drug-drug interactions. Should any updates to the product information be required we will issue an article in our bulletin to healthcare professionals “Drug Safety Update” accordingly.

Yours sincerely,

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