Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

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Dear Mr Osborne

RE: Regulation 28 Report concerning Alana Molly Cutland (doxycycline)

Thank you for your letter dated 5 August 2020, in which you asked the MHRA to provide a response to the Regulation 28 Report to Prevent Future Deaths following the inquest into the tragic death of Miss Alana Cutland.

Your report identified the following matters of concern which fall within the remit of the MHRA.

1. The patient experienced a psychotic reaction as a result of taking doxycycline and there was no mention of the possibility of this in the patient leaflet. If the patient or her parents had been aware of this possible side effect, they might have been able to intervene earlier to avoid her death.

2. The information sent out with doxycycline should be reviewed.

The MHRA as a regulatory agency has a responsibility to ensure 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 (Summary of Product Characteristics, labelling and Patient Information Leaflet, PIL).

As you have noted, the product information for doxycycline does not mention psychotic reactions as a possible side effect. We have conducted a review of the available evidence concerning doxycycline and psychotic reactions and sought expert advice from the Commission on Human Medicine's Pharmacovigilance Expert Advisory Group on the strength of the evidence and whether the doxycycline product information should reflect these events.

As you will be aware, doxycycline has been widely used in the UK since the 1960s for the treatment of various bacterial infections, skin conditions such as acne and as an antimalarial drug. Aside from Miss Cutland's case, as of 2nd September 2020, the MHRA have received five other reports of doxycycline and psychotic disorder, all concerning doxycycline use for bacterial infections. Three of the cases offer possible alternative explanations for the events, either due to previous psychiatric history or concomitant medications that are themselves associated with psychotic reactions. It is

acknowledged that Miss Cutland did not appear to have any history of psychiatric illness, and no other medication was reported. However, her case contains limited details on which to base an assessment of causality with doxycycline.

Overall, these spontaneous ADR reports provide limited evidence on which to base a thorough assessment of causality between doxycycline and psychotic reactions. While under-reporting is a common problem with spontaneous ADR reporting, given that in the context of malaria prophylaxis, doxycycline is often given to healthy people, it may be that we would expect to see more cases of a serious reaction like psychosis if it were a true ADR for doxycycline. In addition, there is no established biological mechanism to explain an association between doxycycline and psychotic reactions and there is little in the way of published literature suggesting a causal link, including a lack of any well-controlled studies.

The CHM Pharmacovigilance Expert Advisory Group advised that overall, the evidence to support a causal association between doxycycline and psychotic disorder was limited considering the cumulative exposure to this drug in the UK which is likely to be in the order of tens of millions of people. The PEAG advised that prior to the possible addition of psychotic type reactions in the doxycycline product information, which may cause patient alarm, further data is needed to enable a more robust assessment. The EAG recommended that the marketing authorisation holder (MAH) for the brand-leader doxycycline product should be requested to propose how this additional data may be collected, for example by investigating the feasibility of conducting a study using electronic healthcare records which compares rates of psychotic reactions following doxycycline, with another antibiotic.

Action being taken by the MHRA

In summary, we have considered the limited available evidence on doxycycline and psychotic reactions and, based on expert advice from the Commission on Human Medicine's Pharmacovigilance Expert Advisory Group, will request that the lead MAH submits a proposal by 30 November 2020 to gather further data on the risk of psychotic reactions following doxycycline.

For your information, Miss Cutland's case has been recorded on our adverse drug reaction database with the Yellow Card reference number **ADR 24432232.**

I will update you once we have evaluated the response of the lead MAH.

In the meantime, we will continue to keep the issue of doxycycline and psychotic reactions under close review.

Yours sincerely

[redacted]

Dr [redacted]
Chief Executive, MHRA

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