Medicines & Healthcare products Regulatory Agency

MHRA

[redacted] PA to HM Coroner for Surrey
HM Coroner's Court
Station Approach
Woking
Surrey
GU22 7AP

[redacted]

[redacted]

Medicines & Healthcare products Regulatory Agency

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

[redacted]

gov.uk/mhra

Dear [redacted],

Regulation 28 Report to Prevent Future Deaths concerning Ann Coles

Thank you for your e-mail of 21 June 2021 regarding a Regulation 28 Report to Prevent Future Deaths following the inquest into the death of Ann Coles. The report raised a matter of concern that there is no requirement for lung imaging to be undertaken when patients are prescribed amiodarone on a long term basis; the consultant cardiologist who treated Ann considered this was a glaring gap in the oversight necessary for the effects of the medication.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the 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).

Amiodarone is an effective medicine for the management of arrhythmia, but it is known to be associated with a number of serious unwanted effects in several organ systems including the eyes, nerves, skin, thyroid, gastrointestinal, lung, heart, and liver. The product information for amiodarone therefore contains extensive warnings and precautions for use, patients must be monitored closely during treatment, and treatment should be initiated and monitored only under hospital or specialist supervision. Additionally, due to its toxicity, the use of amiodarone is now reserved only for the treatment of severe rhythm disorders not responding to other therapies or when other treatments cannot be used.

Amiodarone is available as an oral tablet and as a solution for intravenous (IV) infusion. The SmPC for both formulations describes the symptoms of pulmonary toxicity (i.e. onset of shortness of breath or non-productive cough). The incidence of pulmonary toxicity is known to be lower with IV formulations (where it is reported very rarely, affecting fewer than 1 in 10,000 patients) than for oral formulations (reported commonly, affecting between 1 in 10 and 1 in 100 patients). The SmPC for oral amiodarone notes that onset is usually slow but may be rapidly progressive and whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment.

The product information for oral amiodarone also suggests that consideration be given to chest X-rays before starting therapy, and if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including, where possible, measurement of transfer factor. For IV amiodarone chest X-rays are recommended only when a diagnosis of interstitial pneumonitis is suspected. The PIL reflects this information in patient-friendly language, and section 4 (side-effects) of the PIL for oral amiodarone generally instructs the user to stop treatment and see a doctor or go to a hospital straight away if they experience worsening of respiratory symptoms (which may be common).

The MHRA has conducted a review of this issue and sought independent expert advice on the matter of concern from the Commission on Human Medicines' Pharmacovigilance Expert Advisory Group (PEAG); written advice was also sought from the CHM's Cardiovascular, Diabetes, Renal, Respiratory and Allergy Expert Advisory Group (CDRRA EAG). The PEAG noted that the question of regular pulmonary monitoring has been well considered over many years, but the risks (especially radiation exposure from performing high-resolution computerised tomography [CT] scans) are thought likely to far exceed any benefit. The PEAG also noted that repeated chest X-rays can cause anxiety for patients.

For these reasons, the PEAG did not consider regular chest imaging was advisable or necessary, given that patient-reported worsening of respiratory function is usually the first indicator of pulmonary toxicity. Nevertheless, the PEAG considered that there was scope for improvement in the product information, particularly with respect to the PIL on the seriousness of pulmonary toxicity and the fact this may happen at any time during treatment.

The PEAG also discussed whether additional risk minimisation measures such as a Patient Alert Card would help to inform patients of the risks of treatment and symptoms to be aware of. The PEAG considered that it would be useful to issue a reminder to healthcare professionals on the risks associated with use of amiodarone, the need for monitoring of patients, that patients should be informed and aware of the symptoms of pulmonary toxicity, and that any such symptoms should be reported promptly (and investigated). The PEAG considered that an article in the MHRA's monthly 'Drug Safety Update' bulletin may be an appropriate method to communicate these messages.

The MHRA will now take forward these recommendations. For information, Ms Cole's case has been recorded on our adverse drug reaction database with the Yellow Card reference number [redacted].

I will keep you updated on progress, but in the meantime, we will continue to keep the safety of amiodarone under close review.

Yours sincerely,

[redacted]

[redacted]
Chief Executive
Medicines and Healthcare products Regulatory Agency