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18 July 2014

Re: Miss Akua Anokye-Boateng (Regulation 28 Report to Prevent Future Deaths)

Dear Dr Harris

Thank you for your letter dated 9th May 2014 and bringing to my attention the circumstances of the death of Miss Akua Anokye-Boateng (Regulation 28 Report to Prevent Future Deaths).

On reading your Prevent Future Deaths (PFD) report I identified two distinct points for MHRA to address. These are:

- a) the apparent lack of awareness amongst healthcare professionals that there is the potential for serious gastrointestinal toxicity to occur with short-term use of NSAIDs; and
- b) whether gastrointestinal protective agents should be routinely used alongside NSAIDs in children.

The MHRA has sought the advice of its Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines regarding any necessary actions to address these concerns.

I set out below the actions.

a) *Healthcare professional awareness of the potential for serious gastrointestinal toxicity to occur with short-term use of NSAIDs.*

Following a number of national and Europe-wide reviews of the gastrointestinal safety of NSAIDs, a set of key elements was agreed for inclusion in the Summary of Product Characteristics (SPC) for all non-selective NSAIDs available as prescription only medicines (POM). These key elements include contraindications to use and extensive warnings in relation to the gastrointestinal side effects.

MHRA also formulated a set of key elements for inclusion in the SPC for ibuprofen-containing products available in the UK without prescription as Pharmacy (P) or General Sales List (GSL) medicines.

I attach a copy of the key elements for POM non-selective NSAIDs and also for P and GSL ibuprofen. These were implemented for all relevant products (including products authorised for use in children) in the UK in 2008.

The SPCs for POM, P and GSL NSAIDs including ibuprofen state the following in section 4.4 (Special warnings and precautions for use):

'GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.'

The MHRA and its independent experts consider that this statement in the SPC is sufficient to alert readers to the possibility of serious gastrointestinal side effects occurring early in NSAID treatment. However, we acknowledge that healthcare professionals do not always read the SPC before prescribing, particularly when prescribing commonly used medicines, and your report highlights that there are some healthcare professionals who are unaware of this fact. Therefore we propose to inform and remind healthcare professionals about this through an article in the September 2014 issue of our monthly bulletin 'Drug Safety Update'.

b) Should gastroprotective agents be routinely given alongside NSAIDs in children?

The SPCs for all POM non-selective NSAIDs include a recommendation to use gastro-protective agents (proton pump inhibitors or misoprostol) when prescribing NSAIDs to those at high risk of gastrointestinal side-effects, as follows:

'The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).'

This recommendation is also included in the SPCs for POM non-selective NSAIDs authorised for use in children.

For non-prescription use of ibuprofen in adults and children, a recommendation for the concurrent use of PPIs is not included in the SPC. For those NSAIDs available over-the-counter, the authorised doses are lower than prescription-only products, and the indications only cover short term self-limiting conditions which do not require diagnosis & supervision by a medical practitioner. Patients (or parents of patients) at high risk of gastrointestinal side effects who purchase ibuprofen as an over-the-counter product are advised in the package leaflet to discuss taking these products with their doctor so that they can be properly advised about the need for gastro-protective medicines to be taken at the same time.

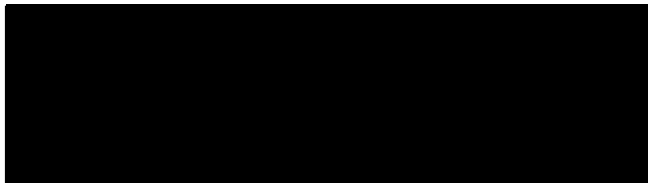
After careful consideration of the details of the case presented in your PFD report, the MHRA and its independent experts do not consider that this case changes the overall benefit-risk balance of ibuprofen in children or warrants a change to the current warnings about the need for gastro-protective agents for prescription only medicines. However, for all NSAIDs we will be strengthening the information for patients/parents provided in the package leaflet on the risk and recognition of gastrointestinal side effects and the action they should take.

In summary, in response to your report under Regulation 28 to Prevent Future Deaths, concerning the death of Miss Akua Anokye-Boateng, MHRA will take the following action to help minimise risk from the gastrointestinal side-effects of NSAIDs:

Proposed action	Purpose of proposed action	Timeline for action
Drug Safety Update (DSU) article (www.mhra.gov.uk/drugsafetyupdate)	To remind healthcare professionals of information already included in the SPCs for NSAIDs, that: <ul style="list-style-type: none"> the GI side-effects of NSAIDs can be serious and life-threatening. Fatalities have been reported. serious GI side-effects can occur with short-term use of NSAIDs serious GI side-effects can occur in people who may be considered to be at low risk, including in children 	Publication in the September 2014 issue of DSU
Strengthen the Patient Information for all NSAIDs with regards to GI risk.	<ul style="list-style-type: none"> To strengthen the NSAID product information provided to patients/parents on the risk. To aid patient/parent recognition of gastrointestinal side-effects and provide information on the action they should take if symptoms arise 	Review and implement changes within 12 months.

I hope that this response addresses your concerns

Yours sincerely



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