Medicines & Healthcare products Regulatory Agency

MHRA

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Dear Dr Cummings,

**Regulation 28 Report concerning Natasha Ednan-Laperouse**

Thank you for your letter of 9th October 2018 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 Natasha Ednan-Laperouse.

Your report listed two matters of concern that fall under the remit of the MHRA and medicines regulation. Your concerns relate to the effectiveness of Epipens, a brand of adrenaline auto-injector carried by at-risk patients for self-administration to treat anaphylaxis before the arrival of the emergency services. Your concerns specifically relate to the adequacy of needle length and adrenaline dose when compared with published guidelines from the UK Resuscitation Council.

Concern (3) – needle length:

It is widely accepted by clinical experts that adrenaline should be delivered into muscle tissue to maximise the chance of recovery from anaphylaxis, a recommendation endorsed by the UK Resuscitation Council. It is clear from the Epipen Summary of Product Characteristics (information for the prescriber), relevant sections from which are displayed in Annex 1, that intramuscular delivery is the intended route of administration: "*EpiPen® auto injector is for adult intramuscular administration.*"

You question whether the exposed needle length of Epipen (16 mm) is adequate to reach muscle in most patients. The adequacy of adrenaline auto-injector needle length was addressed by the MHRA as one aspect of a review in 2014. The available evidence was found to be lacking in some key aspects and the MHRA therefore took this forward as part of a wider European safety review that reported on 25 June 2015. As one of the legally binding conditions following the European safety review, manufacturers were required to disclose the exposed needle length of their adrenaline auto-injector devices in the product information to inform the healthcare professional and patient so they can take this in to account in deciding which device is appropriate for an individual patient. The exposed needle length of the three pens that are marketed in the UK are specified in the Summary of Product Characteristics (SmPC) and patient leaflet, and are as follows: Epipen 0.3 mg (16 mm), Jext 300 mcg (15 mm), Emerade (23 mm).

For clarification, the preferred needle length of 25 mm that you refer to in your report is recommended by the UK Resuscitation Council in the context of anaphylaxis treatment by healthcare professionals, when adrenaline is recommended to be administered by manual intramuscular injection with a syringe

and needle, a method not suitable for self-administration. The UK Resuscitation Council had cause to clarify this, in response to recent media reports that had misinterpreted its guidance:

https://www.resus.org.uk/media/statements/statement-on-anaphylactic-guidelines/

Needles that are too long are not without risk: a needle that is too long can strike bone which has been reported to result in needle fracture and, rarely, in injection of adrenaline into the bone cavity which can mimic intravenous delivery. Where a needle is deployed with force, these risks are likely to be higher.

Adrenaline auto-injectors are designed to forcibly deploy a needle, through clothing if necessary to save time, in the immediate period following the onset of anaphylactic symptoms. Auto-injectors are intended to deliver adrenaline into muscle tissue by a combination of both direct needle penetration and propulsive force of the device. The manufacturer of Epipen asserts that the propulsive force of the device will allow adrenaline to reach muscle even if the device needle is deployed subcutaneously.

The European safety review endorsed that delivery of adrenaline into muscle tissue is the preferred way to treat anaphylaxis in the early, time critical, period before the arrival of the emergency services. However, the review considered that the evidence was not sufficiently robust to support the assertion of intramuscular penetration of adrenaline following auto-injector deployment.

The review concluded that adrenaline auto-injectors are in the main effective and undoubtedly save lives but studies in human volunteers were needed to investigate whether the speed and amount of adrenaline taken up into the bloodstream following auto-injector deployment was consistent with intramuscular penetration of adrenaline.

The requirement for clinical studies – in human volunteers - was imposed by the European Commission for all brands of adrenaline auto-injectors marketed throughout Europe. In the UK, this applies to the three brands of adrenaline auto-injectors that are marketed: Epipen, Jext and Emerade.

Your principal concern is with the Epipen brand given that Natasha failed to respond to two Epipen auto-injectors. The administration of a second adrenaline auto-injector 5 to 15 minutes after the first, if the patient has not responded adequately, is recommended in the instructions for use in the product information for prescriber and patient.

The review of clinical study results for Epipen undertaken by the MHRA and other competent authorities throughout Europe commenced on 15th September 2018. The MHRA raised questions which the company is currently addressing and will result in further information being submitted for evaluation. Regulatory action will be taken as necessary on completion of the review.

For illustrative purposes, clinical study results for the Jext 300 mcg device, submitted prior to the Epipen data, are summarised below. You should be aware that results cannot be extrapolated between different brands of adrenaline auto-injector given that the rate and extent of adrenaline absorption will not only depend on adrenaline dose and needle length but also on the propulsive force of the device as well as the formulation of the adrenaline solution. Individual clinical study results for each device therefore need to be evaluated. The Jext data nonetheless serve to illustrate the types of measures that can be implemented even in the short term, such as factual disclosure of study data in the SmPC, to inform the prescriber and patient.

The study data for the Jext 300 mcg device were submitted to the UK and other European countries where the product is marketed on 21 December 2017 and the evaluation was concluded on 17 October 2018. This informed subsequent updating of the Summary of Product Characteristics (SmPC) and patient leaflet, Annex 2. The study found that, in subjects with a skin to muscle depth greater than 20 mm, adrenaline absorption into the systemic circulation was slower following Jext compared with manual intramuscular injection (using syringe and needle); moreover, in the same subjects, the overall amount of adrenaline reaching the circulation in the first 8, 16 and 30 minutes – the early, time critical period - was lower following Jext injection compared with manual intramuscular injection (these results are

available to the prescriber in section 5.2 of the SmPC – see Annex 2). As a consequence additional warnings have now been implemented in section 4.4 of the SmPC that patients with a thicker subcutaneous fat layer may be at increased risk of an inadequate response and may therefore be more likely to need a second injection. Disclosure of clinical study data to the prescriber within the SmPC, with appropriate specialist clinical guidance, will enable translation of the evidence into clinical practice to inform a decision on suitability of the Jext 300 mcg auto-injector for a particular patient, or whether an alternative device may be advisable. A full report on the studies is expected to be published by end December 2018 by Sweden, the Competent Authority coordinating the evaluation.

Results for Emerade, the third brand of adrenaline auto-injector currently marketed in the UK, are expected to be submitted for evaluation in February 2019. This delayed submission date was agreed by the European Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) due to local ethical committee requirements for screening of patients.

It is foreseen that the evaluation of results for all adrenaline auto-injectors marketed in the UK (Epipen, Jext and Emerade) will be completed during 2019. The availability of data on exposed needle length for all devices, together with the results of clinical studies, will allow an informed decision to be taken on prescribing and advice given to patients. When all study data are available, an over-arching evaluation is intended, to inform whether further measures may be required, that may include a recommendation for longer needle lengths.

Additional outcomes from the European safety review recommended for implementation in the meantime were:

- Recommendations for improved training and educational materials for patients, carers and healthcare professionals in the use of adrenaline auto-injectors.

- Improvements to the product information for prescriber and patient, including strengthening of the recommendation that patients should carry two auto-injectors to enable a second injection if there has been an insufficient response within the first 15 minutes; and reinforcement of the need for family members, carers and teachers to be properly trained in use of the patient's auto-injector.

- A requirement for disclosure of exposed needle length for the respective devices in the product information to inform the healthcare professional and patient.

- These outcomes have been implemented for all adrenaline auto-injector products sold in the UK.

The MHRA has in the meantime published updated advice on the use of adrenaline auto-injectors to patients and their carers:

https://assets.publishing.service.gov.uk/media/5b644e25ed915d377695c83d/AAI-PDF-v4.pdf

Concern (4) – adequacy of adrenaline dose in Epipen:

You question whether a 300 mcg dose of adrenaline – delivered by the adult presentation of Epipen - is adequate to treat anaphylaxis, given the UK Resuscitation Council recommendation that 500 mcg is the dose recommended to treat anaphylaxis.

A discrete, efficacious dose of adrenaline for the emergency treatment of anaphylaxis is not defined. The Resuscitation Council guidance for a 500 mcg dose refers to the dose administered by a healthcare professional (by manual intramuscular injection with a syringe and needle) and is not their recommended dose for adrenaline auto-injector self-administration. In a healthcare setting, a second dose of 500 mcg adrenaline is recommended to be administered after 5 minutes if the patient is not responding. An experienced specialist could also treat anaphylaxis with repeated bolus doses of 50mcg of intravenous adrenaline or may initiate intravenous infusion of adrenaline according to the response. In the healthcare

setting described above, cardiovascular monitoring can be initiated due to the risk of dysrhythmia with high dose adrenaline.

The above treatment regimens are not appropriate in the circumstance where a patient needs to self-administer their adrenaline-autoinjector prior to the arrival of emergency services. In the same clarification statement referred to above
https://www.resus.org.uk/media/statements/statement-on-anaphylactic-guidelines/
the Resuscitation Council clarifies the basis of their recommendation for a 500 mcg dose:
"With regards to dose recommendations, we would like to stress that 500 mcg is the dose healthcare professionals should give to patients over 12 years of age and is not, as has been incorrectly quoted, an RC (UK) recommendation for the provision of adrenaline through auto-injectors."

Although a single Epipen dose in the adult presentation delivers 300 mcg of adrenaline, patients are advised to carry two adrenaline auto-injectors at all times and that a second injection should be given 5 to 15 minutes after the first injection if there has been an inadequate response. The authorised instructions for use therefore allow an adrenaline dose of 600 mcg to be self-administered.

An early lack of response to a first injection cannot, from the available evidence, be predicted with any degree of reliability for a given patient; this underpins the MHRA's continuing recommendation that patients should carry two auto-injectors, which was reinforced in the European safety review. An early lack of response should also be distinguished from the phenomenon of biphasic anaphylaxis that can occur several hours later after an apparently good initial response to emergency treatment. A risk of biphasic anaphylaxis is one reason patients must summon an ambulance even if there has been an apparently good response to auto-injector administration.

Conclusion

The MHRA has, as outlined, taken action in undertaking a review of adrenaline auto-injectors, and has progressed this within Europe, following which a number of outcomes including improved training, additional risk minimisation measures and factual disclosures within the product information have been implemented. The review concluded that adrenaline auto-injectors are in the main effective and undoubtedly save lives but studies in human volunteers were required to determine whether the speed and amount of adrenaline taken up into the bloodstream following auto-injector deployment is consistent with intramuscular penetration of adrenaline. The MHRA is presently undertaking a rigorous evaluation of the clinical study data for each brand of adrenaline auto-injector as and when it is submitted, and will ensure any necessary measures are taken in order to increase the effectiveness of adrenaline auto-injectors in the emergency treatment of anaphylaxis. If necessary, the prescribing information for each auto-injector will be updated as an immediate measure as soon as conclusions on the data have been reached. When data on all products are available – anticipated during 2019 – an over-arching evaluation will be conducted by the MHRA that will inform the need for any further measures.

I will write to you following the completion of the evaluation of the clinical data for Epipen to inform you of any recommendations or regulatory actions that may be deemed necessary to protect public health.

Yours sincerely

Dr Ian Hudson
Chief Executive

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