Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions

Overall summary of the scientific evaluation

Auto-injectors were invented in the 1960s following military research in the United States of America (USA). They were originally used for the administration in the field of atropine, the antidote to nerve agents in biological weapons. The first adrenaline auto-injectors (AAI) were developed and introduced into the medical market approximately 25 years ago in the USA. Adrenaline auto-injectors are indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to e.g. insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) undertook a review of all authorised adrenaline auto-injectors to evaluate the most effective site for injection, the clarity of instructions for use as well as the most appropriate auto-injector needle length for ensuring intramuscular (IM) delivery of the adrenaline injection. A key finding of the review was that there is no robust evidence that the administration devices deliver adrenaline intramuscularly in all patients. Variability in skin-to-muscle depth (STMD), gender, needle length and the device mechanism itself are important factors which determine whether the route of delivery is IM or SC. The matter was then referred to the Committee for Medicinal Products for Human Use (CHMP) for a review under Article 31 of Directive 2001/83/EC.

The use of adrenaline to treat anaphylaxis is established as the recommended first-line treatment. The efficacy of adrenaline in the treatment of anaphylaxis is well-supported by anecdotal and retrospective evidence. The safety of adrenaline is also well-established, and it has demonstrated a particularly strong safety profile with intramuscular (IM) administration. The preferred route of administration in an emergency situation has been established as IM, although intravenous administration may be indicated in severe cases. Published clinical data indicate that the rate of absorption is prolonged if the adrenaline is delivered subcutaneously (SC).

The CHMP has considered the totality of the available non-clinical and clinical evidence on the delivery of adrenaline from adrenaline auto-injectors and on whether the product information contains clear and detailed instructions for appropriate use. The CHMP considered also the results of consultations with healthcare professionals, experts and the Pharmacovigilance Risk Assessment Committee (PRAC).

It is widely accepted that IM delivery is superior to SC delivery in achieving the rate of rise and levels of plasma adrenaline that are most effective to treat anaphylaxis. However, there is insufficient evidence to ensure, even under optimal circumstances, IM delivery of adrenaline to all patients with the currently available auto-injectors authorised in the EU and, even if the medicine is delivered IM, that exposure from a single injection will be sufficient. If IM delivery is insufficient with one injection, administration of a second injection is recommended.

Most of the evidence for penetration of adrenaline into the tissue relies on non-clinical data using a gelatin model or a porcine model. While these non-clinical models have demonstrated that the adrenaline is projected beyond the tip of the needle to a greater or lesser extent the CHMP was of the view that it remains questionable how representative of the human tissue these models are.

Results from PK studies (Simons, 1998[1], 2001[2]) support the guidelines recommendation (e.g. UK Resuscitation Guideline) that an intramuscular injection is the preferred route of administration in the treatment of anaphylaxis as a rapid response is important in ensuring a non-fatal outcome.

[1] F. Estelle R. Simons, MD, FRCPC, Janet R Roberts, MD, FRCPC, Xiaochen Gu, PhD, and Keith J. Simons, PhD. Epinephrine absorption in children with a history of anaphylaxis. Journal of allergy and clinical immunology. January 1998
[2] F. Estelle R. Simons, MD, FRCPC, Xiaochen Gu, PhD, and Keith J. Simons, PhD. Epinephrine absorption in adults: Intramuscular versus subcutaneous injection. Journal of allergy and clinical immunology 108(5); 2001, 871-873

The main clinical data available focus on demonstrating the skin-to-muscle depth (STMD) in adults and children and the CHMP noted that there is inconsistency across the studies with some finding no correlation between STMD and Body Mass Index (BMI) or weight (Song (2005)[3], Stecher (2009)[4]) and others finding a correlation (Bhalla (2013)[5], Bewick (2013)[6]).

However, there is agreement that in general STMD is greater than the length of the needles of currently available adrenaline auto-injectors in many patients, both adult and child.

The STMD is only one factor affecting whether or not the adrenaline reaches the muscle layer. The CHMP agreed that there are many factors that may affect whether the adrenaline is delivered to the muscle or the subcutaneous tissue when an adrenaline auto-injector is used.

The needle length is another factor and the UK Resuscitation Council Guidelines do suggest a 25mm needle is optimal for intramuscular injection; however the CHMP noted that these guidelines are written for use in the hospital setting where healthcare professionals will generally inject the adrenaline using a manual needle and syringe, not an auto-injector.

Other factors such as the mechanism of action (spring loaded or not) and method of administration (swing and jab or place and press) of the device, the angle of placement on the skin and the force used to activate the device also play a part. The CHMP noted the inconsistency amongst studies as to the part played by compression of the tissue. Some investigators are of the opinion that even when the needle length is shorter than the STMD, IM injection is still possible as the physical compression of subcutaneous tissue by the force of the device can help to overcome the deficit in needle length. On the other hand, other investigators express an opinion that compression may preferentially involve muscle rather than subcutaneous tissue and therefore the needle deficit is not overcome by compression. The barrier of the fascia lata – the fibrous tissue surrounding the muscle – also needs to be considered. Until these uncertainties can be resolved, there is a need for more definitive evidence in humans of the speed and extent of delivery of adrenaline into the circulation following use of different adrenaline auto-injectors, from which it may be possible to infer site of delivery.

The CHMP acknowledged that patient/carer compliance with the use of the auto-injectors is also very important as evidenced by the study by Brown J et al (2015)[7]. The fact that 15% of mothers were unable to 'fire' the auto-injector successfully supports that patients' training tools need to be improved and that training needs to be repeated at regular intervals. The CHMP agreed that proper training of both patients/carers and healthcare professionals and comprehensive educational materials are of paramount importance.

The CHMP noted the lack of clinical evidence from randomised, controlled trials, due to the logistical and ethical problems involved with conducting such trials in emergency situations, particularly with a placebo control. However, the CHMP was of the view that PK and PD studies in healthy volunteers representing the broad range of phenotypes, or imaging studies in healthy volunteers to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via an adrenaline auto-injector device could be considered.

[3] Song T, Nelson M, Chang J, et al. Adequacy of the epinephrine auto-injector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy Asthma Immunol 2005;94:539-542
[4] Dawn Stecher, Blake Bulloch, Justin Sales, Carrie Schaefer and Laine Keahey. Epinephrine Auto-injectors: Is Needle Length Adequate for Delivery of Epinephrine Intramuscularly? Paediatrics. 2009, 124(1):p65-70
[5] Bhalla, M.C., B.D. Gable, J.A. Frey, M.R. Reichenbach, and S.T. Wilber, Predictors of epinephrine autoinjector needle length inadequacy. Am J Emerg Med, 2013.
[6] Daniel C. Bewick, MD, Neville B. Wright, MD, Richard S. Pumphrey, MD, Peter D. Arkwright, MD, DPhil. Anatomic and anthropometric determinants of intramuscular versus subcutaneous administration in children with epinephrine autoinjectors. J Allergy Clin Immunol Pract Month 2013. Clinical Communication
[7] Brown J, Tuthill D, Alfaham M et al. (2013) A randomised maternal evaluation of epinephrine autoinjection devices. Paediatr. Allergy Immunol. 00:1-5.

The CHMP sought the advice of experts on the feasibility of conducting imaging or PK studies or any other trials or tests that could be performed as well as the advice of the PRAC on potential databases or other data sources that might hold information on actual device usage.

The experts consulted unanimously agreed that a PK study in humans would be useful in order to gain information on the optimum parameters of administration; the group also noted the possibility to collect PD data in this same study. The PRAC considered that there were no identified data sources that would permit a formal epidemiological approach for assessing actual usage or device failure of adrenaline auto-injectors in the EU.

The CHMP noted that generally there is a large degree of consistency between the product information for the different auto-injectors in particular as regards main messages such as to seek emergency medical assistance immediately after a single administration, the use with caution in certain patient populations and that adrenaline should be administered intramuscularly in order to maximise the possibility of a positive outcome in the treatment of anaphylaxis. However, the CHMP considered that few points merit further clarification.

The CHMP therefore recommended amendments to the product information, in order to reflect the uncertainties in whether a single administration would suffice for any given episode and advise that patients are prescribed two pens which they should carry at all times, to include a recommendation for immediate associates of patients to be trained to use the AAI and to include information on the needle length. The CHMP also recommended further risk minimisation measures, including educational materials, to be submitted and agreed via risk management plans. The educational materials include but are not limited to a training device, instructional audio-visual material and a checklist for prescribers aiming to facilitate the discussion between the prescriber and the patient and to provide sufficient information on the optimal way of use, administration and storage of the product.

Furthermore, the CHMP imposed a PK/PD study in order to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via an adrenaline auto-injector device and encouraged the possibility for a study to assess the effectiveness of the proposed risk minimisation measures and the conduct of an observational study to assess usage and incidence of lack of efficacy and device failure.

The CHMP concluded that the benefit-risk balance for adrenaline auto-injectors remains favourable subject to the agreed changes to the product information and the above-mentioned additional risk minimisation measures.

Grounds for the CHMP opinion

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for adrenaline auto-injectors.
- The CHMP considered the totality of the available non-clinical and clinical data to inform whether adrenaline administered via an auto-injector is delivered intramuscularly or subcutaneously, including submissions by marketing authorisation holders, consultations with healthcare professionals, experts and the Pharmacovigilance Risk Assessment Committee (PRAC).
- The CHMP considered that the efficacy of adrenaline in the treatment of anaphylaxis is well-supported by anecdotal and retrospective evidence and that the safety of adrenaline is also

well-established, and it has demonstrated a strong safety profile particularly with IM administration.

- The CHMP considered that the preferred route of administration of adrenaline in an emergency situation has been established as IM, although intravenous administration may be indicated in severe cases.
- The CHMP considered that there are multiple factors that may affect whether adrenaline is delivered to the muscle or the subcutaneous tissue when an adrenaline auto-injector is used such as the needle length, the mechanism of action of the device, the angle of placement on the skin, the force used to activate the device and the patient/carer compliance. Training and education of both patients/carers and healthcare professionals was considered of paramount importance.
- The CHMP noted that the product information for the different auto-injectors would benefit from an update to include warnings and precautions on uncertainties in whether a single administration would suffice for any given episode and advise that patients are prescribed two pens which they should carry at all times, training of immediate associates of patients and inclusion of information on the needle length.
- The CHMP concluded that there was a need for further risk minimisation measures such as educational materials to be submitted and agreed via risk management plans. The CHMP also concluded on the need for a PK/PD study to be conducted in order to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via an adrenaline auto-injector device.

The CHMP concluded that the benefit-risk balance for adrenaline auto-injectors remains favourable subject to the conditions to the marketing authorisations and taking into account the amendments to the product information and other risk minimisation measures recommended.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the CHMP recommends the variation to the terms of the marketing authorisation for all medicinal products referred to in Annex I and for which the amendments of the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III.

The conditions affecting the marketing authorisations are set out in Annex IV.