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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Adrenaline auto-injectors (AAIs)

International non-proprietary name: adrenaline (epinephrine)

Procedure number: EMEA/H/A-31/1398

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Information on the procedure

1.1. Referral of the matter to the CHMP

The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) undertook a national review of all authorised adrenaline auto-injectors. All the auto-injector products approved in the UK have been authorised based on bibliographic data relating to the known efficacy and safety of intramuscular (IM) adrenaline by manual needle and syringe in the treatment of anaphylaxis. The summary of product characteristics (SmPC) of all the auto-injectors state that the route of administration is IM as this elicits the most rapid response. However, a key finding of the review was that there is no robust evidence that the administration devices deliver the adrenaline intramuscularly in all patients. Variability in skin-to-muscle depth (STMD), gender, needle length and the administration device mechanism itself are important factors which determine whether the route of delivery is IM or SC. The latter would result in longer response time and thus might be less effective in the treatment of an anaphylactic event.

On 02 April 2014 the United Kingdom, therefore, initiated a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of adrenaline auto-injectors and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

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.

Anaphylaxis is a serious, generalised or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal and it has sudden onset (minutes to a few hours). It is characterised by rapidly developing, life-threatening problems involving the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea); and/or circulation (hypotension and/or tachycardia). In most cases, there are associated skin and mucosal changes. It needs prompt initial treatment with epinephrine (adrenaline) injected intramuscularly.

Adrenaline is the natural active sympathomimetic hormone from the adrenal medulla. It stimulates both the α - and β -adrenergic receptors. Adrenaline has a potent vasoconstrictive effect through its α -adrenergic stimulation. This effect counteracts the vasodilatation and increased vascular perfusion, leading to low intravascular flow and hypotension, which are the main pharmacotoxicological effects in the anaphylactic shock. By stimulating β -receptors in the lungs, adrenaline produces a potent bronchodilator effect with relief of wheezing and dyspnoea. Adrenaline also alleviates pruritus, urticaria and angioedema and may relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

The 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 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.

In view of this, the United Kingdom considered that it is in the interest of the Union to refer the matter to the Committee for Medicinal Products for Human Use (CHMP) and requested that it gives its opinion under Article 31 of Directive 2001/83/EC on whether the marketing authorisations for these medicinal products should be maintained, varied, suspended or revoked.

An overview of the relevant information for the discussion is presented hereinafter, including non-clinical and clinical data submitted by marketing authorisation holders (MAHs) and the results of consultations with healthcare professionals, experts and the Pharmacovigilance Risk Assessment Committee (PRAC).

2.2. Non-clinical aspects

Two main non-clinical models (i.e. ballistic gelatine and porcine models) are presented below in the context of their usefulness for assessing the performance of injector pens in delivering adrenaline to the muscle layer.

2.2.1. Results

Ballistic gelatine

Ballistic gelatine is reported as being designed to simulate living soft tissue (Nicholas and Welsch, 2004)¹. It was first used in 1960 and various techniques were used to measure the kinetic energy of a projectile travelling through a block of gelatine. Early models were not compared to living tissue in a quantitative or reproducible way. Fackler (1984)² analysed bullet fragmentation in gelatin and in living pork tissue (hind legs). Although the paper did not include specific comparisons between gelatin and animal tissue, this paper subsequently was cited as reference for gelatin being an approximate or equivalent substitute for animal tissue. A later paper by Fackler and Malinowski (1985)³ states that the depth of penetration measured in living swine leg muscle was reproduced in the gelatine within 3%. These findings and the convenience of using non-animal or non-cadaveric tissue appear to have led to the use of gelatine on its own.

A study comparing three injector pens was reported by Schwartz and Seeger (2012)⁴. Three adrenaline auto-injectors (AAI) designed to deliver 0.3 mg adrenaline were compared: Jext and EpiPen, which are cartridge-based AAIs, and Anapen, a syringe-based AAI. They were tested for, amongst other features, the injection depth and estimated volume of black ink delivered into ballistic gelatine. The mean maximum injection depths in gelatine within 10 seconds were 28.87 mm (SD 0.73) for Jext, 29.68 mm (SD 2.08) for EpiPen and 18.74 mm (SD 1.25) for Anapen. The length of the EpiPen and Jext needles

¹ Nicholas N, Welsch J. Ballistic Gelatin. Report of Institute for Non-Lethal Defense Technologies. February 2004

² Fackler ML, Surinchak JS, Malinowski JA, Bowen RE. Bullet fragmentation: a major cause of tissue disruption. J Trauma. 1984 Jan; 24(1): 35-9.

³ Fackler ML, Malinowski JA. The wound profile: a visual method for quantifying gunshot wound components. J Trauma. 1985 Jun; 25(6): 522-9.

⁴ Schwartz A and Seeger H. Pharma Consult GmbH, Vienna, Austria. Comparison of the robustness and functionality of three adrenaline auto-injectors. Journal of Asthma and Allergy 17 August 2012

is 14.3 mm and the mean distance between skin and muscle in women (n = 50) has been estimated at 14.8 mm. The exposed length of the Anapen needle is 8.9-9.9mm.

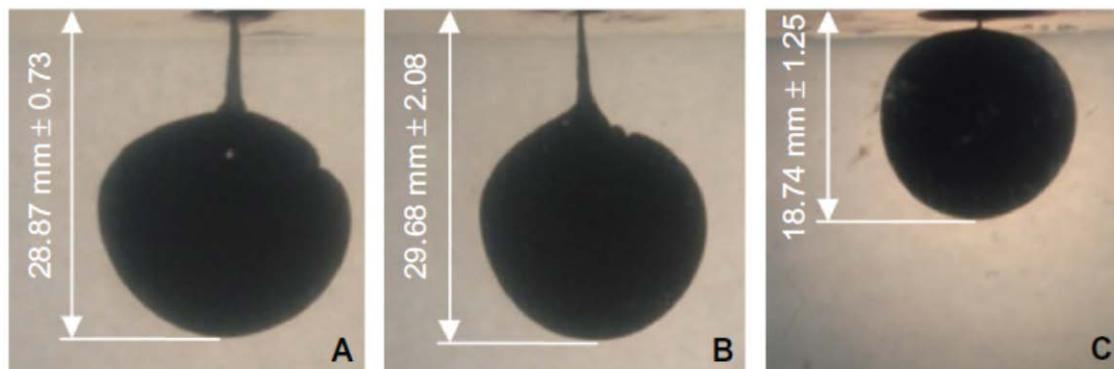


Figure 1 (Schwartz and Seeger (2012)). Photographs showing the total injection depth into gelatine 10 seconds after activation of Jext (A), EpiPen (B), and Anapen (C), measured as the vertical distance from the surface of the gelatine to the lowest part of the ink area using digital image processing.

This study demonstrated that the adrenaline delivered via cartridge-based AAIs was delivered to a depth almost twice that of the length of the needle.

Porcine models

A study was conducted by the US military on the depth of penetration into live porcine thighs achieved by the EpiPen to address the question of its performance in obese patients (Ferguson et al, 2008)⁵. Adrenaline from 21 EpiPen devices was mixed with methylene blue as a colour tracer and triggered into the lateral thigh of 21 pigs. The results showed that with an exposed needle length of 14.3 mm, the mean \pm SD delivery depth from the skin to the muscle was 26.9 ± 5.4 mm ($p < 0.0001$), consistent with approximately twice the needle length. All injections delivered epinephrine beyond the needle length and into muscle. However in these pigs the depth of the fat layer was only ~ 7 mm.

Another study presented by Schwartz (2012)⁶ assessed the injection characteristics of three AAIs (EpiPen, Jext and Anapen) using a cadaver pork model to replicate human thigh tissue. The adrenaline solution of 14 AAIs (3 syringe-based 500 microgram dose, 4 syringe-based 300 microgram dose, 4 new cartridge-based 300 microgram dose, 3 traditional cartridge-based 300 microgram dose) was replaced by the contrast agent, Jopamiro 300. Fresh pork shoulders (30°C) were cut into pieces of approximately 100 mm x 100 mm. The AAIs were individually placed at the centre of the test tissue, activated and held in place for 10 seconds.

Immediately after the injection, the test tissue was placed on a Computer Tomography (CT) scanner and pictures were taken. The skin-to-muscle distance and maximum injection depth reached by the

⁵ Ferguson JW, Merrill, N, Song TT, 2008. Madigan army Medical Center Tacoma, WA. Delivery Depth of Epinephrine by Auto-injector into Subcutaneous Tissue of Swine. Journal of Allergy and Clinical Immunology, Volume 121, Number 2. Abstract 98.

⁶ Schwartz, A; Comparison of the injection depth of 3 adrenaline auto-injectors in a pork shoulder model. Presented by Andreas Schwartz as a poster at the European Academy of Allergy & Immunology Congress in 2012.

contrast agent were determined for each CT image. After use, the exposed needle length was measured with callipers.

The CT scans showed that both EpiPen and Jext (both cartridge based AAI) achieve a maximum injection depth which is deeper than the exposed needle length. The maximum injection depth in pork shoulder samples by syringe-based AAIs ranged from 10.00 to 14.80 mm and from 22.45 to 35.05 for cartridge-based AAIs. Also the CT images revealed that all Jext and EpiPen samples achieved an IM injection but Anapen with its shorter, smaller gauge needle failed to inject more than 5 mm beyond the exposed length and in some cases the scans showed that it did not achieve an IM injection. The depth of fat ranged from 3.90 mm ('lean') to 19.40 mm ('fat').

The results indicate that the contrast media was injected beyond the needle tip into muscle from the cartridge based AAI despite the skin-to-muscle distance (STMD) being in excess of exposed needle length. It should be noted that the contrast media has a higher viscosity than adrenaline solution and therefore would have reduced velocity.

Song et al (2013)⁷ demonstrated in a study with methylene blue dye injected into pig thigh that EpiPen could deliver adrenaline beyond the needle tip (cadaveric pig model). It was demonstrated that the auto-injector's needle length of 14.3 mm is adequate to deliver adrenaline to the IM tissues in all pigs studied. All of the injections had SC tissue depth greater than 14.3 mm in the pig model. The mean SC tissue depth of 27.8 mm was 94.4% beyond the auto-injector's needle length. The findings of the study suggest that propulsion and compression may help deliver adrenaline beyond the length of the needle and into the IM tissue, even in those patients who are obese.

The advantages of this model over the pork shoulder model are that the viscosity of the solution will be practically identical to the adrenaline solution meaning that the injection depths will be greater as can be seen in the results compared to the pork shoulder method. However the methylene blue injection method does not allow for quantification of injection volume and will be less precise for depth measurement due to tissue movement during dissection of the injection site.

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.

2.2.2. Discussion

Most of the evidence for penetration of adrenaline into tissue relies on non-clinical data using a gelatin model or a porcine model.

Regarding the ballistic gelatine, the CHMP noted that the study by Schwirtz and Seeger (2012) demonstrated that the adrenaline delivered via cartridge-based AAIs was delivered to a depth almost twice that of the length of the needle. However, the Committee was of the view that while the conditions and preparation of the gelatine have been standardised to some extent, and can be used to compare the behaviour of projectiles within that limited context, the model cannot be regarded as fully representative of living tissue, primarily because it is homogeneous rather than heterogeneous. The different types and textures of animal tissue cannot be regarded as being adequately simulated in a gelatine alone system.

Regarding the porcine model, the CHMP noted that the delivery depths reported by Schwirtz (2012) for EpiPen and Jext are in broadly the same range as those published by Ferguson (2008) (mean of 26.9

⁷ Song, TT; Merrill, NL; Cole, JW; Delivery depth of epinephrine by auto-injector into the subcutaneous tissue of pig; *Ann Allergy Asthma Immunol* 2013;11:143-145.

mm), and confirm that the contents of the AAI can be delivered to a depth greater than the exposed length of the needle. The study by Schwirtz (2012) also suggests that, at least in cadaver pork the adrenaline can penetrate muscle even if the STMD is greater than the length of the needle.

The pig as an animal model for human skin is generally accepted as being the most representative and it is commonly used in pharmaceutical development for local tolerance and skin penetration studies. Given the difficulty in generating clinical data on injector pens, the use of the pig for this purpose is considered appropriate and the most valid model currently available. However, the CHMP was of the view that the porcine models involve cadaver porcine tissue so it is not known how representative of live human tissue with its vasculature intact this may be. The studies using the porcine model have given conflicting results with some studies demonstrating penetration of adrenaline given via the cartridge-based AAIs into muscle despite the STMD being greater than the exposed length of the needle. Others have suggested that the fascia lata between the subcutaneous tissue layer and the muscle will prevent penetration into the muscle if the needle tip does not penetrate into muscle.

2.3. Data on efficacy

The CHMP considered all available data, including data submitted by the MAHs mainly consisting of published literature as evidence for intramuscular or subcutaneous delivery of adrenaline from their respective administration devices. However, there are no direct data demonstrating the site of delivery of adrenaline from any of the currently available auto-injectors.

2.3.1. Results

Pharmacokinetics (PK)

Studies have been performed to compare the pharmacokinetics of adrenaline administered by the SC and IM routes.

Simons et al (2001)⁸ conducted a prospective, randomised, blinded, placebo-controlled, 6-way crossover study of intramuscular versus subcutaneous injection of epinephrine in healthy allergic men aged 18-35 years. The objective of the study was to provide information regarding the optimal route and site of epinephrine injection in adults.

During the course of the study, each participant received 4 injections of epinephrine 0.3 mg (0.3 mL) and 2 injections of saline solution (0.9% NaCl, 0.3 mL) through use of a variety of injection routes and sites. Epinephrine USP I: 1000, 0.3 mg (0.3 mL) was injected either IM into the vastus lateralis muscle or the deltoid muscle or SC in the deltoid region.

To ensure blinding, all injections were given by a nurse not otherwise involved in the study, and at each visit both the thigh and upper arm sites were covered after the injection.

⁸ 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

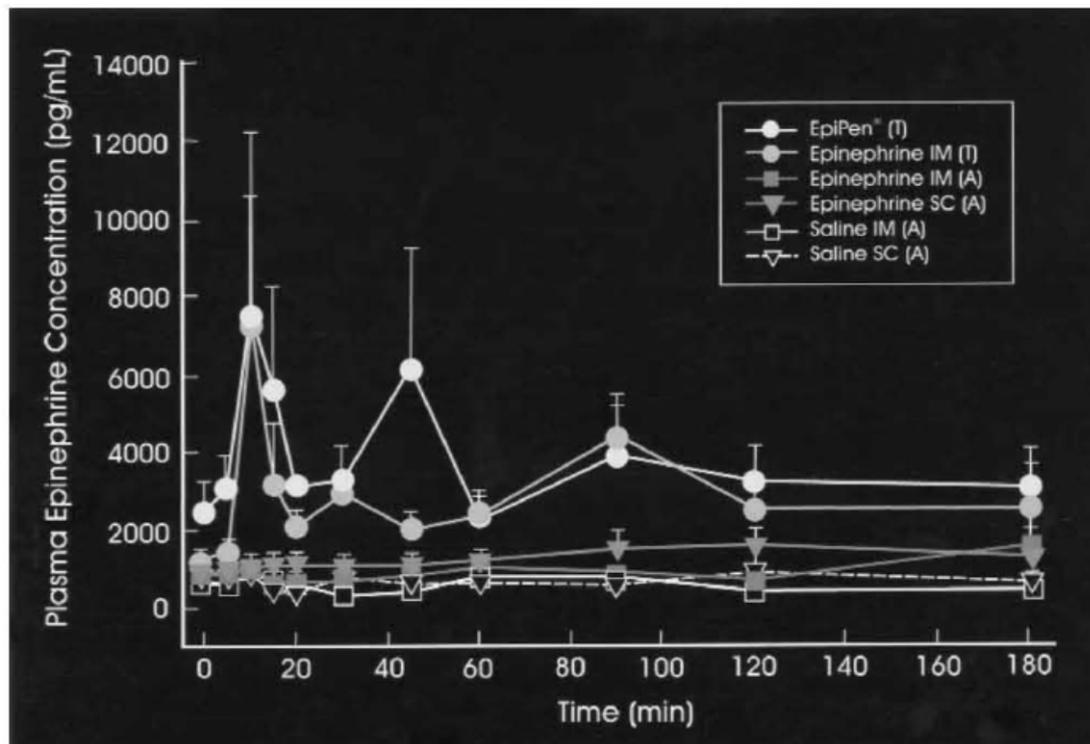


Figure 2 (Simons et al (2001)). Mean plasma epinephrine concentrations versus time are shown after administration of an identical 0.3mg (0.3ml) dose of epinephrine by IM or SC injection in 2 different sites. T; Thigh; A upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of 0.9% saline solution (0.3ml) in the upper arm. The plasma epinephrine concentrations shown were calculated by averaging (mean \pm SEM) the epinephrine concentrations at each sampling time for each route and each site of injection.

The results showed a swift increase in plasma levels of epinephrine following IM injection into the thigh (vastus lateralis muscle), and the C_{max} was much greater than levels achieved from an IM or SC injection into the arm (deltoid muscle). Unfortunately the study did not investigate SC injection into the thigh but the plasma levels seen following the injection with EpiPen were very similar to those achieved following an intramuscular injection using a needle and syringe. The T_{max} for the IM injection was around 10 minutes.

A further study by [Simons et al \(1998\)](#)⁹ in 17 children measured the pharmacokinetics of adrenaline following subcutaneous injection (9 children) and intramuscular injection (8 children).

The study was a prospective, randomised, blinded parallel group study in children with a history of anaphylaxis. The subcutaneous injection was administered via needle and syringe while the intramuscular injection was administered using EpiPen auto-injector (exposed needle length 14.3mm).

In the nine children who received a SC injection the mean maximum plasma concentration of adrenaline was 1802 ± 214 pg/ml achieved at a mean time of 34 ± 14 minutes (range 5 to 120 minutes). Only two of the children achieved a maximum concentration of adrenaline by 5 minutes. In the eight children who received intramuscular injection via EpiPen the mean maximum concentration of adrenaline was 2136 ± 351 pg/ml achieved at a mean time of 8 ± 2 minutes, which was significantly

⁹ 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

faster than the mean time at which maximum plasma concentrations of adrenaline were achieved using the SC route.

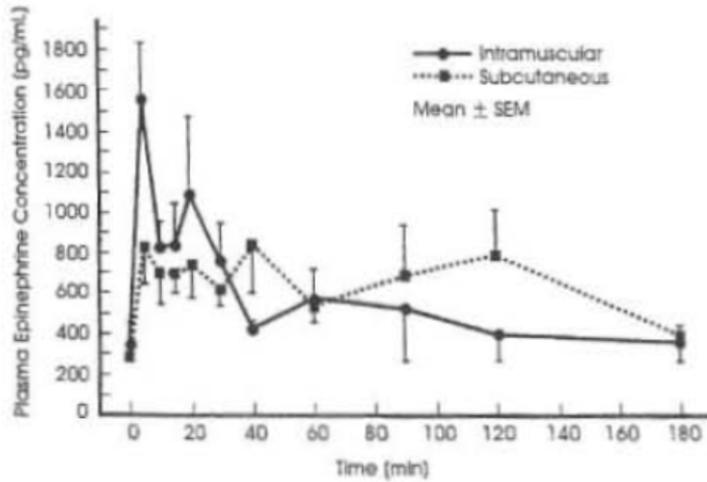


Figure 3 (Simons et al (1998)). Mean plasma adrenaline concentration versus time after injection of adrenaline subcutaneously or intramuscularly

The results of this study support the intramuscular route as the optimal route of administration of adrenaline in the treatment of anaphylaxis.

Skin-to-muscle depth

There are concerns that, owing to the increasing obesity (Body Mass Index (BMI) ≥ 30) of the population in the European Union, the needle lengths in the currently licensed adrenaline auto-injectors may not be adequate to deliver the dose of adrenaline to the muscle tissue of the thigh.

To date, various investigations into the skin-to-muscle depth (STMD) have been conducted in both adults and children. Skin thickness (ST) and subcutaneous tissue (SCT) have been evaluated using either computed tomography (CT) or ultrasound methodologies. [Song et al's \(2005\)¹⁰](#) analysis of skin-to-muscle depth in adults via CT showed that the mean \pm SD distance from skin-to-muscle was 1.48 ± 0.72 cm for women and 0.66 ± 0.47 cm for men, respectively.

¹⁰ Ted T. Song, DO; Michael R. Nelson, MD, PhD; James H. Chang, MD; Renata J. M. Engler, MD; Badrul A. Chowdhury, MD, PhD. Adequacy of the epinephrine auto-injector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol.* 2005;94:539–542

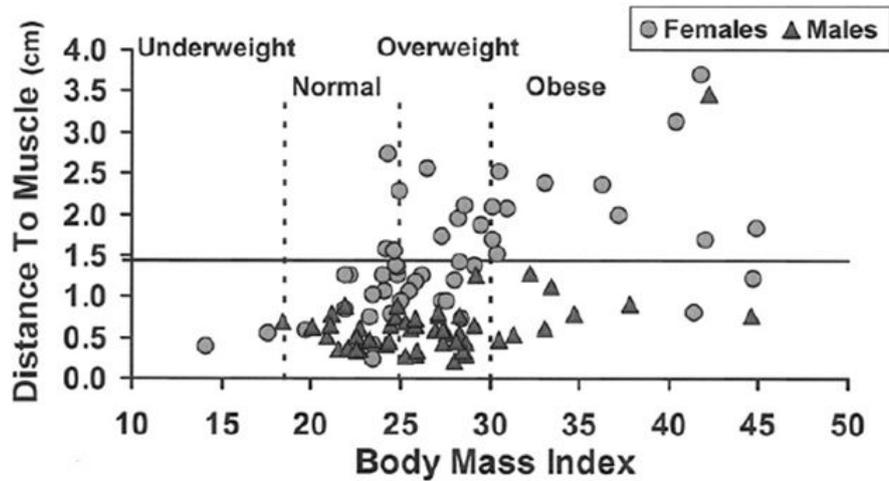


Figure 4 (Song et al (2005)). Scatterplot of the distance to muscle vs body mass index for men and women. Dashed vertical lines are drawn to identify the body mass index categories.

The horizontal line in figure 4 indicates the length of the epinephrine auto-injector needle length of 1.43 cm. Individuals above the 1.43-cm line would most likely receive subcutaneous epinephrine.

Bhalla et al (2013)¹¹ used ultrasound imaging to show significant associations between compressed muscle depth and BMI ($r = 0.48$; $p < 0.001$) and between compressed muscle depth and thigh circumference ($r = 0.62$; $P < 0.001$) (Bhalla (2014))¹².

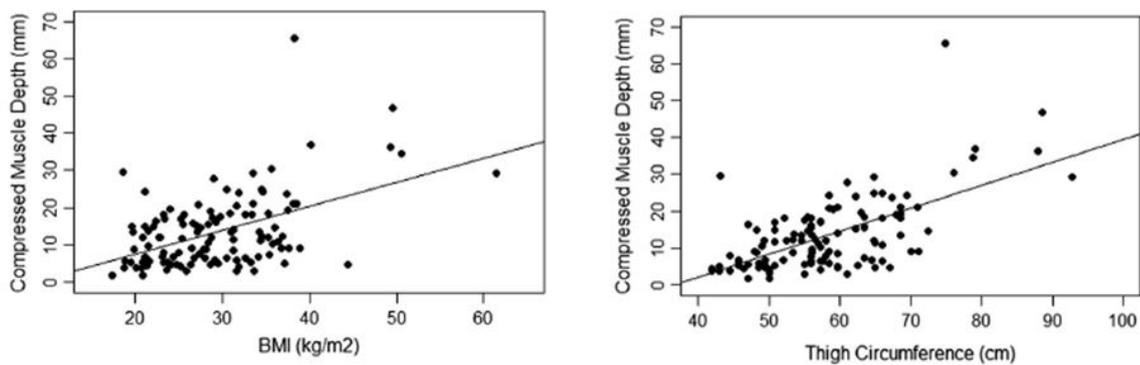


Figure 5 (Bhalla (2013)). BMI and compressed muscle depth (left) – Thigh circumference and compressed muscle depth (right)

A study conducted by Gibney et al (2010)¹³ in 388 US adults patients with diabetes having diverse demographic features (in three BMI subgroups: < 25 , $25 - 29.9$, and ≥ 30 kg/m^2), measured the skin thickness (ST) and subcutaneous adipose layer thickness (SCT) via ultrasound at four injection sites. A

¹¹ Bhalla, M.C., B.D. Gable, J.A. Frey, M.R. Reichenbach, and S.T. Wilber, Predictors of epinephrine auto-injector needle length inadequacy. *Am J Emerg Med*, 2013.

¹² Bhalla MC. Response to comments on "Predictors of epinephrine autoinjector needle length inadequacy". *Am J Emerg Med*. 2014 May; 32(5):474.

¹³ Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. *Curr Med Res Opin*. 2010 Jun; 26(6): 1519-30.

multivariate analysis showed the ST did not differ by clinically significant degrees in demographically diverse adults with diabetes whereas the SCT had a wider range.

Conversely, SCT varied substantially by certain characteristics (body site, BMI, gender) and less by race and age. The mean (\pm SD) subcutaneous thickness in the thigh was 10.35 ± 5.6 mm. And, the SCT was directly related to BMI—a change of 10 BMI units accounted for approximately 4 mm change in SCT.

In children, measurement of obesity, including weight ($p=0.004$), BMI ($p<0.001$) and waist circumference ($p<0.001$), but not age or sex, were predictive for STMD (Bewick, 2013)¹⁴. Analysis of subcutaneous (SC) fat thickness in 100 children aged between 2 months and 6 years revealed that the thickness of SC fat in the thigh ranges between 3 and 26 mm. In male patients, mean SC fat thickness was about 11 – 12 mm, in female patients between 11 and 15 mm (Lippert, 2008)¹⁵.

Stecher et al (2009)¹⁶ analysed the skin-to-muscle depth in children between one and almost 13 years. The average distance from skin to muscle in these children was 9.24 mm (range 3.1 to 21.6 mm). In the group of children who weighed ≥ 30 kg the distance from skin to muscle in this group was 12.2 mm (range 5.7 to 41.9 mm).

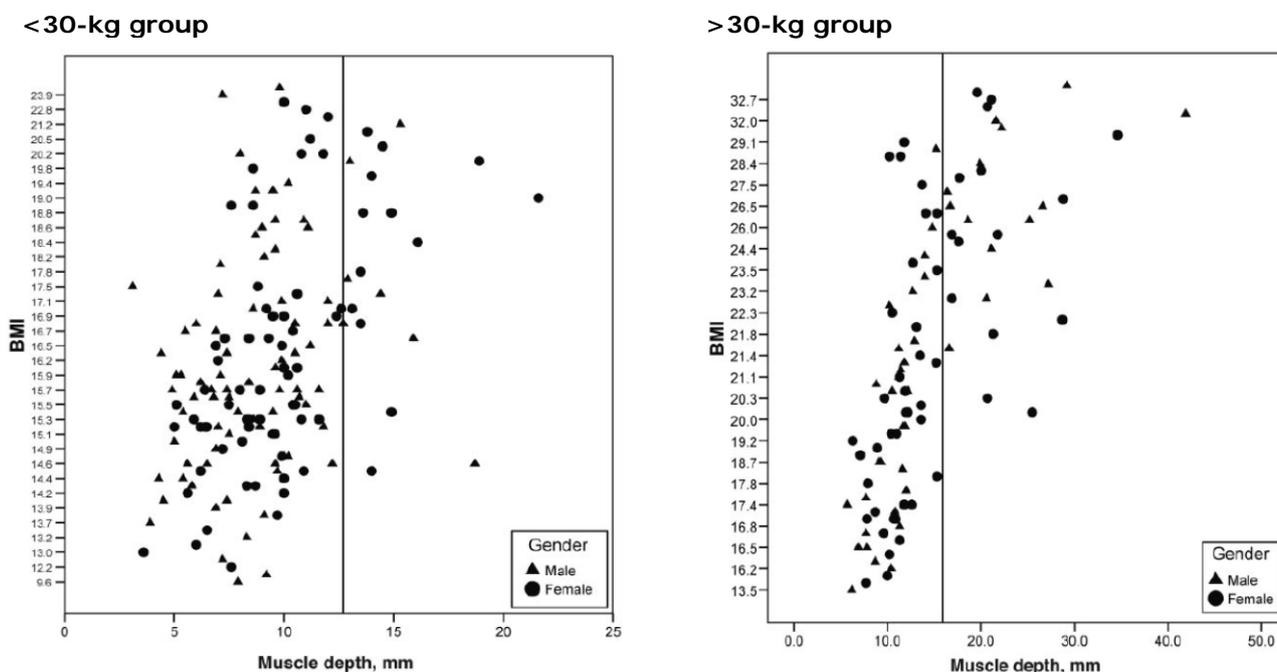


Figure 6 (Stecher et al (2009)). Scatter plot of depth to muscle from skin surface vs BMI. The vertical line represents the length of the needle (12.7 mm)

If adequate delivery of adrenaline to individuals with high BMI was a clinical issue, it might lead to greater need for a second adrenaline injection. This question regarding BMI was recently addressed by Rudders et al (2012)¹⁷ in a chart review of 321 emergency department (ED) cases of confirmed

¹⁴ 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

¹⁵ Lippert WC, Wall EJ. Optimal intramuscular needle-penetration depth. *Pediatrics*. 2008 Sep; 122(3):e556-63.

¹⁶ 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

¹⁷ Rudders SA, Geyer BC, Banerji A, Phipatanakul W, Clark S, Camargo CA, Jr. Obesity is not a risk factor for repeat epinephrine use in the treatment of anaphylaxis. *J Allergy Clin Immunol* 2012; 130(5): 1216-1218.

anaphylaxis consisting of a total of 261 children and 60 adults. Within this group of patients, 57 (18%) were overweight and 69 (22%) obese. When adjusting for age and gender, there was no significant association between obesity (vs. no obesity) and patients receiving ≥ 2 doses of adrenaline (OR 1.22; 95% CI 0.77, 1.93; $p=0.40$).

In a study from the University of Worcester, (EAACI) [Hobbins et al \(2014\)](#)¹⁸ found that Jext and EpiPen do not have sufficient needle length to administer IM adrenaline in the vastus lateralis in 68% of the patients who had already been prescribed AAIs for a clinical history of anaphylaxis in UK.

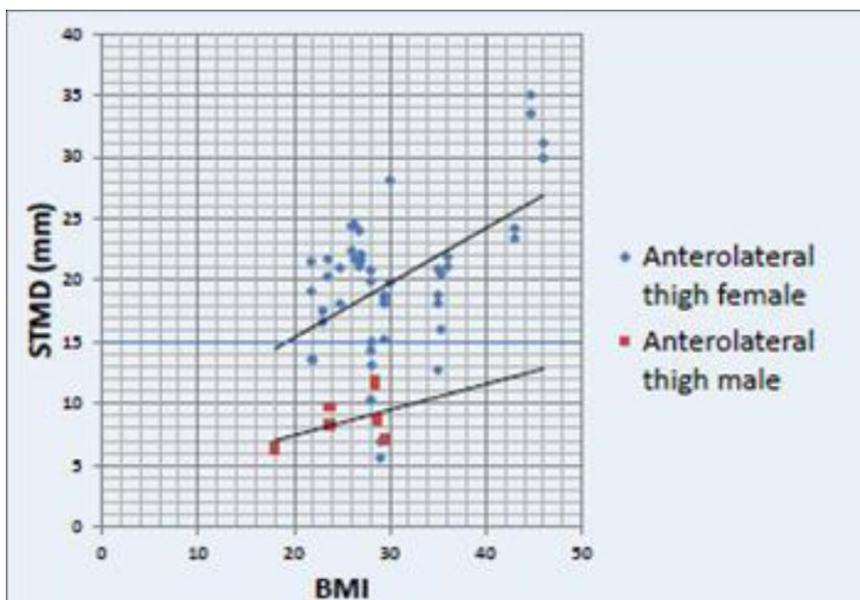


Figure 7 (Hobbins et al (2014)). Scatter plots showing the relationship between STMD, BMI and gender. Blue line equals the mean length of an EpiPen needle (15.02 mm).

Mechanism of action and administration

A MAH stated that in “adrenaline auto-injectors (AAIs) the adrenaline solution is pressurised to varying degrees depending on individual auto-injector device design and construction. This device-dependent phenomenon causes the solution to be expelled beyond the needle tip to varying degrees as displayed with EpiPen ([Song et al, 2013](#))¹⁹. The cartridge-based technology of some AAIs allows for a stronger spring-mechanism than is feasible with syringe-based devices and generates sufficient activation and propulsive forces to ensure that penetration of a wide range of clothing and tissues is reliably achieved, and that IM delivery of adrenaline is achieved within seconds²⁰.”

Skin compression

The study conducted by Bhalla et al cited above, included subjects with a mean BMI of 29.2 kg/m² and the mean uncompressed muscle depth was found to be 18.9 mm. However, the mean compressed muscle depth was 13.4 mm ([Bhalla et al, 2013](#))¹¹. This results in a reduction of muscle depth by compression of approximately 30%. This compression factor corresponds with findings by Song et al. Song published results of an analysis of CT that showed that the mean (\pm SD) distance to muscle was

¹⁸ Hobbins, S., Johnstone, J., O’Hickey, S., Subcutaneous tissue precludes intramuscular injection in the majority of patients prescribed epinephrine auto injectors. EAACI 2014, Copenhagen, 2014; Poster 698.

¹⁹ Song TT, Merrill NL, Cole JW. Delivery depth of epinephrine by auto-injector into the subcutaneous tissue of pig. *Ann Allergy Asthma Immunol.* 2013 Aug;111(2):143-5.

²⁰ Frew AJ. What are the ‘ideal’ features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? *Allergy* 2011; 66: 15–24.

14.8 ± 7.2 mm for women and 6.6 ± 4.7 mm for men. To trigger the EpiPen auto-injector, the patient has to apply a minimum pressure of 2 to 8 lb. Investigations by [Song et al \(2005\)](#)¹⁰ showed that 8 lbs of weight decreased the distance to muscle by 25% in a woman and by 19% in a man.

In [Wang et al's \(2013\)](#)²¹ study comparing needle penetration probabilities of AAIs, the probability of the needle tip reaching muscle in the population described by Gibney et al was estimated. Using an exposed needle length of 15.24 mm, calculations for the probability of the needle tip reaching muscle used the formula $\Phi\left[\frac{s-\mu}{\sigma}\right]$, where Φ is the cumulative distribution function, s is the needle length, and μ and σ are the mean and standard deviation, respectively, of the combined thickness of skin and subcutaneous tissue. Probabilities were calculated on the basis of absolute tissue thickness across a range of compression factors (i.e. 0%-35%), allowing for evaluation of different approaches to the triggering of an adrenaline auto-injector from "place and hold" to "swing and firmly push". When compression is applied, the probability of the AAI needle tip reaching muscle is given by the equation $\Phi\left[\frac{s-\mu(1-c)}{\sigma(1-c)}\right]$, where c is the compression fraction.

A MAH stated that "for the same compression fraction, patients with thicker tissue will be compressed more compared with patients with thinner tissue". Triggering of the EpiPen auto-injector is dependent on the application of up to 8 pounds of pressure, producing an approximately 19% to 25% compression factor in men and women, respectively. In this study by Wang et al, assuming 25% compression, the EpiPen auto-injector needle tip is anticipated to reach muscle in approximately 100%, 95%, and 83% of patients with BMI <25, 25 to <30, and ≥30 kg/m², respectively. With no compression, the needle tip of the same size is expected to reach muscle in approximately 93%, 76%, and 54% of patients with BMI <25, 25 to <30, and ≥30 kg/m², respectively, with the EpiPen auto-injector" (Figure 8).

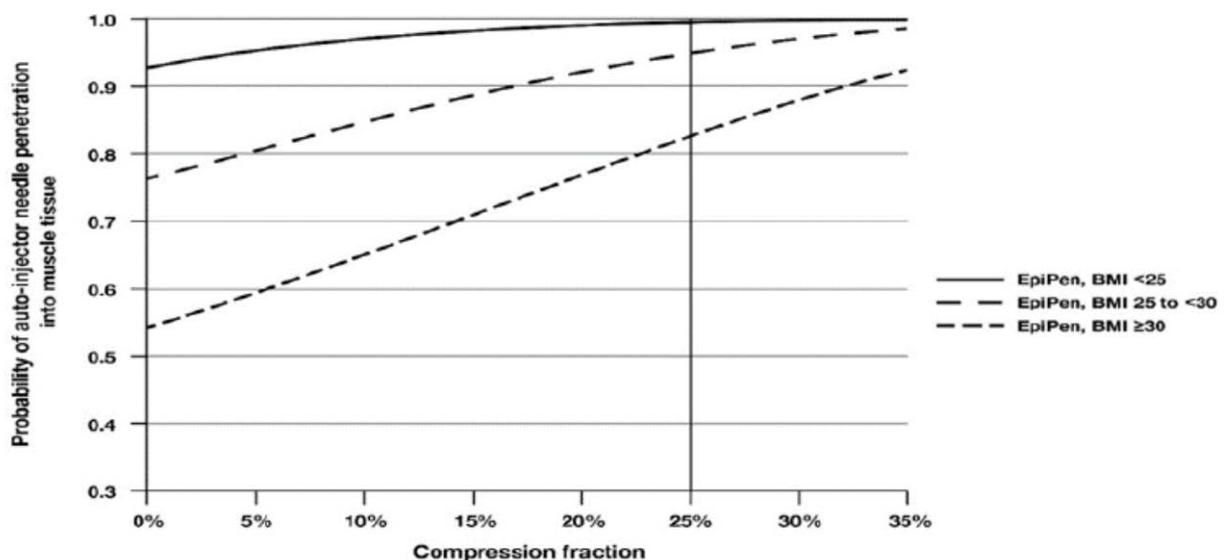


Figure 8. Probability of AAI needle penetration into muscle tissue stratified by BMI

One of the MAHs estimated the skin and subcutaneous thickness after compression using the equation from Wang et al and data from Gibney et al and provided the following results:

²¹ Wang C, Wolf R, Cavanaugh PF. Comparison of needle penetration depth probabilities of two epinephrine auto-injectors. *Allergy Asthma Proc.* 34[5], 483. 2013.

- Assuming an injection depth of 90% beyond the needle length (from non-clinical models) and considering the reduction of the distance to muscle under exertion of the pressure required to activate the auto-injector (20% in men and 25% in women) the mean injection depth becomes 3.4 cm in men and 3.6 cm in women.
- Stecher analysed the skin-to-muscle depth in children between 1 and almost 13 years. The average distance from skin to muscle in these children was 9.24 mm (range 3.1 to 21.6 mm). In the group of children who weighed ≥ 30 kg the distance from skin to muscle in this group was 12.2 mm (range 5.7 to 41.9 mm).
- The auto-injector used in children is assumed to reach an injection depth of 60% beyond the needle length [from non-clinical models²²]. Together with a 20% muscle compression, the injection depth becomes 2.5 cm.
- So the MAH concluded that virtually all children with a weight >30 kg adequately receive adrenaline intramuscularly by the auto-injector.

Patient compliance/competence

An important parameter that needs to be considered is how competent patients, or carers of patients, are in actually using AAI. In 2013 [Brown, J et al \(2015\)](#)²³ studied maternal competence in using the epinephrine auto-injectors EpiPen and Anapen training devices following the authors' standard anaphylaxis training. One hundred mothers participated and their performance was evaluated using ten predetermined criteria. A substantial proportion of mothers (15% overall) were not able to successfully 'fire' these training devices (Anapen 4% and EpiPen 26%). Only 22% of mothers overall were able to perform all ten procedures completely successfully (Anapen 32% and EpiPen 12%). Chi-squared analysis showed a significantly higher proportion of mothers correctly performing all Anapen specific procedures than EpiPen (OR=14.24, $p \leq 0.0001$).

2.3.2. Discussion

Pharmacokinetics

The CHMP noted that the studies performed to compare the pharmacokinetics of adrenaline administered by the SC and IM routes concluded that IM administration in the thigh results in quicker time to peak plasma concentration (T_{max}) and higher peak plasma concentration (C_{max}) compared with the SC route in the arm (Simons 1998⁹, 2001⁸). Regardless of the variability associated with adrenaline plasma exposure, rapid IM injection of adrenaline after the appearance of symptoms is vital to optimise treatment and minimise mortality (Simons, 1998). This faster absorption via IM administration favours this route of administration over subcutaneous (SC) administration (Resuscitation Council (UK); 2008).

Skin-to-muscle depth

The CHMP commented that based on latest available data, more than half (52%) of the adult population in the European Union are overweight or obese. The prevalence of overweight and obesity

²² Sattler I, Schwirtz A. Anaphylaxis treatment: are adrenaline auto-injectors fit for purpose? Poster Allergologie 2010

²³ Brown J, Tuthill D, Alfaham M et al. (2013) A randomised maternal evaluation of epinephrine autoinjection devices. Paediatr. Allergy Immunol. 00:1-5.

among adults exceeds 50% in no less than 18 of 27 EU member states. On average across EU member states, 17% of the adult population is obese²⁴.

Therefore, the CHMP expressed concerns whether the needle lengths in the currently authorised adrenaline auto-injectors in the EU are adequate to deliver the dose intramuscularly. The CHMP discussed the advantages and disadvantages of employing a longer needle length on the AAI devices to promote IM injection and acknowledged that the development of other administration devices with longer needles would require extensive redesign of the medical device, pharmaceutical development and substantial changes to the manufacturing process with the long lead-in time and testing this would require. A more feasible approach would be to identify the patients in which the current administration devices are more appropriate but in order to do so the precise depth of penetration of the adrenaline injection from these devices needs to be ascertained and as a result the CHMP stressed the need to generate data through further studies.

Regarding the study by Rudders et al (2012) the CHMP commented that the calculation of the OR has not been presented but when the comparison is made looking at the percentage of patients requiring 1 or 2+ doses in each weight category (as presented by the MAH) there is little difference across the groups:

BMI category	Overall (N = 321)	1 dose (n = 267)	2+ doses (n = 54)
Underweight; n (%)	27 (8)	24 (9)	3 (6)
Healthy weight; n (%)	168 (52)	139 (52)	29 (54)
Overweight; n (%)	57 (18)	48 (18)	9 (17)
Obese; n (%)	69 (22)	56 (21)	13 (24)

However, looking at the percentage of patients within each weight category requiring 2+ doses there is a trend towards an increased percentage requiring 2+ doses as the weight increases:

Underweight:	11.1%
Healthy weight:	17.3%
Overweight:	15.7%
Obese:	18.8%

The CHMP was of the view that this would suggest that, contrary to the conclusion of the authors, overweight and obese patients are more at risk of receiving a subcutaneous injection than those of healthy weight.

The CHMP noted that the study from the University of Worcester confirms the findings of Song et al and Stecher et al that many adults have a skin-to-muscle depth greater than the 15 mm length (14.3 mm exposed length) of the EpiPen and Jext AAIs. However, the CHMP was of the opinion that it does not provide any evidence of the site where adrenaline is delivered from an auto-injector in the real life situation.

Mechanism of action and administration

The CHMP stated that even though the rationale of activation and propulsive forces project the adrenaline beyond the needle length and into the muscle has been accepted to date, there is no consistent and compelling evidence to support this. Data provided by the MAHs show that a layer of clothing such as denim has no noticeable difference in the performance and penetration of the injection when compared to that directly into bare skin. However, really thick clothing, e.g. through denim seam has been shown to have a reduced injection depth when compared to that directly into bare skin. The CHMP commented that given that the testing sample was small (n=3) it is not known whether a statistically significant difference exists between the two scenarios. No data were provided by the

²⁴ OECD Library. Overweight and obesity among adults. <http://www.oecd-ilibrary.org/sites/9789264183896-en/02/07/index.html?itemId=/content/chapter/9789264183896-26-en> Accessed 07/08/2014

MAHs to support the statement that an IM injection is achieved within seconds and the CHMP was of the view that it is likely that no such data exist.

Skin compression

One of the MAH's has used Wang et al's equation to calculate the probabilities of intramuscular injection in patients with varying BMIs assuming the degree of compression likely with the force needed to activate the auto-injector. The CHMP commented that the results as shown on figure 8 demonstrate that in the worst case scenario, with no compression, even patients with normal BMI (<25) would not all receive intramuscular injections (see figure 6). However, the CHMP stated that this scenario is not relevant in the clinical setting as some compression will occur due to the force needed to fire the auto-injector.

Regarding the use of the auto-injector for children the conclusion of the MAH was considered incorrect by the CHMP as from the STMD calculations by Stecher et al an injection depth of 25mm would penetrate the muscle in virtually all children with a weight <30kg but not all children with a weight ≥ 30 kg.

Patient compliance/competence

The CHMP found it concerning that 15% of mothers overall could not "fire" these devices correctly despite a one-to-one demonstration and was of the view that this identifies a need for a more 'user-friendly' device and adequate training. Training and education of both the patients/carers and of the healthcare professionals on how these products should be used and stored was considered by the CHMP as one of the key factors affecting the site of delivery.

Overall discussion

Results from PK studies (Simons et al) support the Resuscitation Guidelines recommendation 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.

The main clinical data have concentrated on demonstrating the skin-to-muscle depth (STMD) in adults and children and again there is inconsistency across the studies with some finding no correlation between STMD and BMI or weight (Song, Stecher) and others finding a correlation (Bhalla, Bewick).

However, there is agreement that in general STMD is greater than the length of the needles of currently available AAIs in many patients, both adult and child. The STMD is only one factor in whether or not the adrenaline reaches the muscle layer; 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 will also play a part. Proper training of both patients/carers and healthcare professionals and comprehensive educational material are also of paramount importance. There is also disagreement 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.

Unfortunately no clinical studies into the efficacy of adrenaline delivered via the adrenaline auto-injectors in the treatment of an anaphylactic episode have been conducted due to ethical and logistic issues of conducting a study in such an urgent and life-threatening situation. However, it is crucial that further data are generated to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via an adrenaline auto-injector device.

2.4. Data on safety

The CHMP did not require the MAHs to submit any safety data. The safety of adrenaline is well-established, and it has demonstrated a particularly strong safety profile with IM administration. In addition, no new safety concern emerged from the overall submitted data.

3. Expert consultation

3.1. Consultation of healthcare professional organisations

The CHMP also obtained additional information from the healthcare professionals' perspective on the identification and handling of at risk patients as well as on additional proposals to minimise the possibility for SC administration which could be less effective in an emergency situation.

The healthcare professional organisations commented that in the current clinical practice options for the needle length depend on age and weight and should be based on the STMD of the patient. Patients at increased risk of receiving SC administration can be identified using ultrasound to assess the STMD.

For at risk patients, longer needles could be prescribed, the device could be used at a different area (e.g. anterior thigh) and two devices could be prescribed on a regular basis and should be carried by the patient at all times.

The healthcare professional organisations commented that pharmacokinetic studies with the currently available AAI devices would be helpful to allow understanding what plasma adrenaline levels are achieved with different devices in patients of different ages and sizes. This would help guide prescribing and perhaps clarify if devices with longer needles need to be developed. The importance of appropriate training that must be repeated at any consultation was also highlighted.

The views and proposals from healthcare professional organisations were taken into account by the CHMP in its opinion.

3.2. Consultation of an ad hoc expert group meeting

An *ad hoc* expert group meeting composed mainly of allergists, pharmacokineticists and radiologists was convened on 23 January 2015 at the request of the CHMP to gain insight on the experts' view on the factors that make it more likely to receive a SC rather than an IM administration, on the feasibility of conducting imaging or PK studies or on any other trials or tests that could be performed.

The expert group was of the view that multiple factors could influence the site of delivery. These factors could be either clinical (e.g. needle length, STMD, correct dose) or human (e.g. training, incorrect handling of the device under stress in an emergency situation). The importance of regular dialogue between patients and their doctors to ensure monitoring and tailored guidance was highlighted. All experts stressed the need to generate further, more robust data in humans in order to

determine for the particular devices the relationship between each of these factors and the site of delivery which would help in tailoring treatment to the individuals.

Regarding the conduct of imaging studies, the group commented that the clinical relevance of each method discussed (e.g. ultrasound, magnetic resonance imaging, computed tomography, nuclear medicines with radiolabelled tracers) needs to be carefully considered given the limitations identified for each one of them. Hence the group proposed as an alternative to consider including imaging techniques in a PK/PD study.

The group unanimously agreed that a PK study in humans would be useful in order to gain information on the optimum parameters of administration. The experts were in favour of a randomised, blinded, cross-over PK study with a placebo arm as adrenaline is an endogenous substance. It was proposed to investigate needle length and possibly different injection sites in subjects stratified by BMI (obese and non-obese), age, gender and metabolism and to collect data on the effect of the IM and SC injections. The group also noted the possibility to collect PD data in this same study such as monitoring the change in heart rate and blood pressure (systolic and diastolic).

3.3. Consultation of the PRAC

The CHMP sought the advice of the PRAC on potential databases or other data sources that might hold information on actual device usage.

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. Even if data sources were identified, the limitations of such studies would mean that they could only be exploratory in nature and robust conclusions would be precluded. In addition, the PRAC considered that a simple case series approach would be preferable for gaining further data on the reasons for adrenaline device failure, if there are adequately documented case reports.

4. Risk management

4.1. Pharmacovigilance activity

4.1.1. Imposed PK/PD study

The CHMP recommended that each MAH conducts an exploratory PK/PD study with their adrenaline auto-injectors to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via their adrenaline auto-injector device.

The MAHs should reflect on the following points in the protocol of their study:

- Performed in healthy volunteers using existing products and doses, including a treatment group with adrenaline delivered by syringe to promote IM injection.
- A cross-over design (possibly incomplete-block) to facilitate within-patient comparisons where appropriate, in addition to between-patient comparisons.
- Different sites of injection, e.g. mid-thigh versus distal thigh.
- Patient cohort sufficient to be able to provide data on exposure by patient characteristics considered most influential for determining exposure (BMI, STMD, gender and age).

- Correlating measures of exposure to PD markers to characterise the onset of physiological changes (heart rate, blood pressure).

In addition the MAHs should follow the protocol outlines that were submitted during the referral procedure with all amendments provided by the EMA and are requested to also include the following in their protocols:

- Measurement of BMI and thigh circumference with a view to investigating correlation between these parameters and STMD or thigh type.
- Rate of absorption should be included as an important PK characteristic to be assessed.
- A means of allowing for endogenous adrenaline should be included (considering both baseline measure and background physiological changes that would result from the process of using an auto-injector); preferably a placebo arm or an accepted and pre-specified method for baseline correction.

The MAHs are strongly encouraged to seek scientific advice from the EMA on the final study protocol.

While the CHMP considered that the individual clinical studies proposed by the MAHs will provide some useful information to understand the behavior of their administration devices it is considered that the most optimum use of the data, when available, would be the inclusion of all data in a Population PK (PopPK) model. Such a model would benefit greatly from the increased range in demographics captured and with all data pooled, this would allow an improved understanding of the variability of the data and a more accurate determination of the important covariates on the exposure, or PD, end points e.g. gender, age, BMI, injection site and device type. The model would also allow simulations to be performed for different covariate categories to determine the need for dose or technique adjustment in some sub-populations and to support dosing recommendations.

4.1.2. Non-interventional studies

The CHMP also discussed the possibility and encourages the MAHs to conduct a study to examine the effectiveness of the risk minimisation measures in place as well as an observational study to assess usage and incidence of lack of efficacy/device failure.

4.2. Risk minimisation activities

4.2.1. Educational materials

Educational measures are necessary in order to ensure that healthcare professionals and patients/carers are able to successfully administer the product based on the instructions in the product information. These should include but are not limited to:

- Training device

The CHMP recommended the development of a training device for both healthcare professionals and patients/carers. This training device should allow prescribers and patient/carers to familiarise themselves with the device and the administration procedure of the prescribed adrenaline auto-injector before its actual use. The training device should mimic the precise step of use of the active device without containing the active substance or a needle and offer the possibility to be reset and used repeatedly.

It should be ensured that the labelling on the training device allows differentiation with the administration device containing the medicinal product in order to avoid a potential mix-up by the patient in an emergency situation. Appropriate warnings, e.g. "For practice only", "Do not use for treatment", "Without needle, without drug" should be placed and highlighted on the training device and be positioned so as to be easily noticed by patients or carers in an emergency situation.

The training device is not part of the medicinal product and should be provided in separate packaging to the auto-injectors' active device.

The package leaflet of the training device and other currently available educational materials, where applicable, should also advise that the training device and the active device should not be routinely carried together to minimise the risk of confusion between the two devices in an emergency situation.

- Instructional audio-visual material

The CHMP recommended the development of instructional audio-visual material easily accessible to healthcare professionals and to patients/carers. This audio-visual material should explain in detail how the product is to be used and the different steps for the administration (e.g. patient positioning, site of administration). The CHMP also recommended that the instruction video be made available on DVD or some other tool so that patients who do not have access to the internet can obtain it. The package leaflet should contain information on the availability of such a video with an address and/or telephone number for patients to contact requesting it.

- Checklist for prescribers

The CHMP recommended that a checklist for prescribers is developed. This checklist is intended to be used by healthcare professionals when prescribing or renewing an adrenaline auto-injector device 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.

In addition to the above, the MAHs should ensure that currently available education material is not only available on websites but also as printed material. The CHMP recommended that national translations of the currently available educational material should present the most relevant emergency number and the one which can be used whilst travelling in the EU. The CHMP also recommended the inclusion in the package leaflet of a QR (quick response) code and a URL to the website where the relevant educational materials are located.

4.2.2. Risk management plan (RMP)

The CHMP concluded that MAHs should submit risk management plans for each adrenaline auto-injector containing the important safety concerns of device failure, accidental injection and lack of efficacy. The CHMP commented that given the approved indication, the major safety concerns should be consistent between the RMPs of all adrenaline auto-injectors as far as possible. The risk minimisation measures, including educational materials must be submitted and agreed via RMPs. Once the RMPs are accepted, updated PL and associated documentation to insert references to the educational materials such as QR code, URL, contact details to request DVD training video should be submitted.

4.2.3. Amendments to the product information

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 routine risk minimisation measures in the form of updates to the product information would be necessary 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 also for immediate associates of patients to be trained to use the adrenaline auto-injector;
- to include information on the needle length.

These changes include amendments to sections 4.2, 4.4 and 6.5 of the summary of product characteristics (SmPC). The relevant sections of the package leaflet (PL) were revised accordingly and were brought in line with the agreed SmPC amendments.

The final agreed wording for the relevant sections of the SmPC and PL can be found in Annex III of the opinion.

It was also agreed that the MAH(s) for EpiPen and associated names would improve the PL diagram in the instructions for use by increasing the size and ensuring that it clearly shows that the injection should be in the antero-lateral aspect of the thigh.

The MAHs shall ensure that the product information changes for adrenaline auto-injectors agreed by the CMDh in May 2014 have been implemented as per the national requirements

(http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/CMDh_Recommendations/CMDh_314_2014_2014_05_AAIs_product_information.pdf).

5. Benefit-risk balance

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) 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.

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 BMI or weight (Song, Stecher) and others finding a correlation (Bhalla, Bewick).

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. 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.

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.

6. Grounds for 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 of the CHMP opinion.

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