Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Epinephrine

MT/W/009/pdWS/001

Rapporteur:	**Herbert M. Lenicker MD, D.C.H., D.Sc., F.C.C.P**
Finalisation procedure (day 120):	14th July 2015

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI.
INN (or common name) of the active substance(s):	Epinephrine (adrenaline)
MAH (s):	See section VI.
Pharmaco-therapeutic group (ATC Code):	C01 CA24
Pharmaceutical form(s) and strength(s):	Ampoules, vials 1mg/ml

I. Executive Summary

The scope of this paediatric worksharing procedure is updating of product information regarding **epinephrine (adrenaline) 1mg/ml (1:1000) injection products only** not any other dilutions and formulations.

SmPC and PL changes are proposed in section **4.2 Posology and method of administration** and in Section **4.4 Special warnings and precautions for use** of epinephrine1mg/ml (1:1000) injection products.

Basing on the assessment of the rapporteur and the comments made by concerned Member States and the recommendations of the European Resuscitation Council (ERC) (2010) and the European Academy of Allergy and Clinical Immunology (EAACI) (2007) it is recommended that the Marketing Authorisation Holder (MAH) may include the additional table of intramuscular (IM) doses of epinephrine for the initial emergency treatment of paediatric anaphylaxis as follows:

Age	Dose of epinephrine1mg/ml (1:1000 solution)
Over 12 years	0.5 mg IM (0.5ml 1:1000 solution)
6 - 12 years	0.3 mg IM (0.3ml 1:1000 solution)
6 months - 6 years	0.15 mg IM (0.15ml 1:1000 solution)
Under 6 months *	0.01mg/kg IM (0.01ml/kg 1:1000 solution)

* The doses are in line with the recommendations of the ERC except for the recommendation for infants under 6 months in which case a more tailored dosage could be administered if there are safety concerns as expressed by some Member States (MSs).

If necessary, these doses may be repeated several times at 5 - 15 minutes intervals according to blood pressure, pulse and respiratory function.
A small volume syringe should be used.

Reviewing the EAACI 2014 Guideline (based on `The management of anaphylaxis in childhood: position paper of the European Academy of Allergy and Clinical Immunology; Allergy 2007; 62: 857-871) quoted by the MAH for the dose of epinephrine (used via auto-injectors) it is recommended that “patients weighing between 7.5 kg (corresponds to weight 6month old baby) and 25kg should receive 0.15mg (0.15ml) epinephrine IM for the emergency treatment of anaphylaxis. This is close to the ERC dosage recommendations.

There is no uniform position adopted regarding IM epinephrine dosage at European level. Even though the generally accepted dose is 0.01mg/kg, there are no studies to support this dosage.

While the dose of 0.01mg/kg body weight can always be used for the initial emergency treatment of paediatric anaphylaxis the additional dosage table is meant to help during an emergency in children when the weight is not known or when the prescriber is not sure of a correct mathematical calculation.

It is recommended by the Rapporteur that apart from the generally accepted dosage of epinephrine 0.01mg/kg an additional dosage table according to age may be included in the Member States (MSs) where the recommended doses are currently in practice. Some MSs may not to wish to include this additional dosage table if it is not relevant to national practice.

The MAH is requested to submit a type IB variation within 60 days from the finalisation of this worksharing procedure in order to be able to include the recommendation in the product information.

Summary of outcome

X **Change:** new safety data from medical literature in section 4.2 and 4.4 of the SmPC of epinephrine (adrenaline) concerns the 1mg/ml (1:1000) injection products only.

1.) **Section 4.2** of the SmPC: An additional table with recommended intramuscular (**IM**) paediatric doses (see below) for anaphylaxis may be included in the Member States where the recommended doses are currently in practice.

Age	Dose of epinephrine1mg/ml (1:1000 solution)
Over 12 years	0.5 mg IM (0.5ml 1:1000 solution)
6 - 12 years	0.3 mg IM (0.3ml 1:1000 solution)
6 months - 6 years	0.15 mg IM (0.15ml 1:1000 solution)
Under 6 months	0.01mg/kg IM (0.01ml/kg 1:1000 solution)

If necessary, these doses may be repeated several times at 5 - 15 minutes intervals according to blood pressure, pulse and respiratory function.
A small volume syringe should be used.

2.) **Section 4.4** of the SmPC to add the following:

The IM route is generally preferred in the initial treatment of anaphylaxis, the intravenous (IV) route is generally more appropriate in the Intensive Care Unit (ICU) or Emergency Department (ED) setting. Epinephrine injection 1:1000 (1mg/ml) is not suitable for IV use. If the epinephrine1:10000 (0.1mg/ml) injection is not available, epinephrine injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of epinephrine must be used with extreme caution and is best reserved for specialists familiar with IV use of epinephrine (adrenaline).

X Paediatric information clarified:

In **Section 4.2 and 4.4** of the SmPC: see above recommendations.

The MAH is requested to submit a type IB variation within 60 days from the finalisation of this worksharing procedure in order to be able to include the recommendation in the Product Information.

II. Recommendation

Type IB variation to be requested from the MAH within 60 days in line with Section I. Executive Summary and Summary of outcome.

III. INTRODUCTION

The scope of this paediatric worksharing procedure is updating of product information regarding **epinephrine (adrenalin) 1mg/ml (1:1000) injection products only** not any other dilutions and formulations.

Since its introduction in 1903 epinephrine (adrenaline) injection has proved to be a valuable, effective medication for use in a variety of severe and serious conditions in emergency settings. It has a history of long established use.

Data packages were submitted by the MAH for paediatric work sharing (PdWS) for the epinephrine procedure number MT/W/009/pdWS/001 in conformity with Article 45 of the Paediatric regulation (EC) 1901/2006 as amended.

No prospective, randomized, double-blind, placebo-controlled epinephrine clinical pharmacology studies have been conducted in infants and children. Dosages used are mainly based on traditional use. Epinephrine has very powerful pharmacodynamic effects. Basing on safety information it appears that dosage errors are relatively frequent. It is essential that more comprehensive paediatric dosage information should be available to guide users for the greater safety of epinephrine injection when used in infants and children.

Basing on the review of published reports during the last two decades there are concerns about the practicality and adequacy of information regarding intramuscular dosage of epinephrine in children. This vital information needs to be more comprehensive in all Summary of Product Characteristics (SmPCs) and package leaflets (PLs). This is necessary in order to create greater awareness of appropriate paediatric dosage to diminish the possibility of dosage errors in emergency situations.

Careful epinephrine dosage using weight and volume for verification of appropriate small volume administration are essential to prevent epinephrine toxicity in infants and children.

In connection with this pdWS procedure MT/W/009/pdWS/001 regarding epinephrine1mg/ml (1:1000) injection the MAH submitted the following documentation in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

The MAH had no relevant data to submit in the context of this Article 45 procedure for the following reasons:

No paediatric clinical studies line listings had been submitted by the MAH back in January 2008 in the context of Art 45 legislation, but only the 3 following publications:

1.) Fischer M. treatment of acute anaphylaxis. BMJ (91995) 311: 731-733

2.) Nadkarni V et al. Paediatric Life Support. Resuscitation (1997) 34: 115-127

3.) Stopfkuchen H. Notfälle in Kindesalter. Wissenschaftliche Verlagsgesellschaft. 3. Auflage, 1988. .S. 24

4.) A short critical expert overview has also been provided. It is very clear and well written. It contained 43 relevant references.

The Submission contained the following documentation:

Module 1
• Module 1.0 Cover letter
• Module 1.4.3 Information about the Expert – Clinical

Module 2
• Module 2.5 Critical Expert Overview

Module 4
• Module 4.3 Literature References

Module 5
• Module 5.4 Literature References

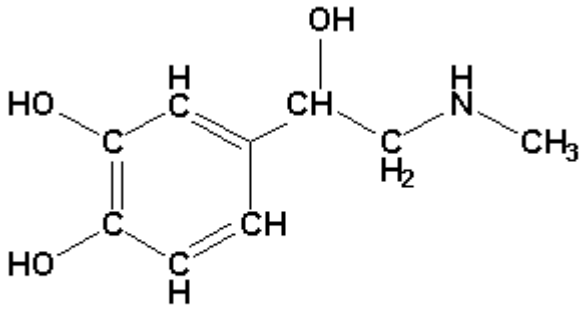
As recommended, as part of the Best Practice Guide on Article 45 Paediatric Regulation EU work-sharing.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

History

In May 1886, William Bates reported the discovery of a substance produced by the adrenal gland in the *New York Medical Journal*. Epinephrine was isolated and identified in 1895 by Napoleon Cybulski, a Polish physiologist. The discovery was repeated in 1897 by John Jacob Abel Jokichi Takamine, a Japanese chemist, independently discovered the same hormone in 1900. In 1901 he isolated and purified the hormone adrenaline from cow glands. It was first artificially synthesized in 1904 by Friedrich Stolz.



Epinephrine

The first approval of epinephrine injection was obtained in Austria on the 15.05.1952.

Epinephrine is referred to traditionally as adrenaline in the United Kingdom (UK).

There is no paediatric formulation of epinephrine1mg/ml (1:1000) injection.

When epinephrine is required in children appropriate portions or fractions of the 1mg/ml (1:1000) of the injection have to be used. Because of the small volumes required in paediatric emergencies accuracy in dosage may be compromised unless a suitable syringe measuring small quantities is used.

Epinephrine injection 1:1000 has to be diluted 1 in 10 when required for IV injection.

Epinephrine injection has to be diluted for intra-tracheal (IT) administration.

Epinephrine injection is also diluted in surgery 1:200,000 for subcutaneous infiltration purposes or for topical application in ear, nose and throat (ENT) operations.

Epinephrine injection is also diluted in surgery 1:200000 for subcutaneous infiltration purposes or for topical application in ENT operations.

IV.2 Non-clinical aspects

1. Introduction

Epinephrine (adrenaline) is an endogenous substance that is produced by the adrenal medulla and has important physiological effects. It is also used pharmacologically as a direct – acting sympathomimetic that acts as a potent agonist on both alpha- and beta-adrenergic receptors, although the effect on beta receptors is more marked at lower doses.

2. Non clinical study(ies)

No relevant nonclinical safety studies in juvenile animals conducted or sponsored by the MAH have been submitted.

There are hardly any non-clinical data and still less any juvenile toxicity studies. The reason may be that epinephrine is considered to be an endogenous substance and has had a long established use**.**

Basing on the clinical expert's report a literature review was performed in Embase (1947 to present) and Medline (1966 to present) databases using the following strategy: (epinephrine or adrenaline) and (adverse drug reaction or drug toxicity or toxicity) limited to juvenile animal, newborn (all used terms are thesaurus Emtree terms).

One experimental study in neonatal pigs was performed by Mauch et al. on the electrocardiographic alterations following intravenous (IV) administration of three different test doses of bupivacaine and epinephrine. This animal model demonstrated that increases in heart rate and T- wave elevation in the ECG during IV application of a common test dose (0.2 ml/kg) of bupivacaine are caused by epinephrine addition at dose of 1:200 000. The authors concluded that. "Although we have chosen the study conditions as close to modern paediatric anaesthesia practice as possible and the pig model is the closest to humans, our results do not fully reflect similar responses in children". No other relevant nonclinical safety information on juvenile animals was identified in the literature.

In conclusion, no relevant nonclinical safety data on juvenile animals are available in internal documentation or in literature which would impact the clinical safety data reported in this procedure.

IV.3 Clinical aspects

1. Introduction

Epinephrine belongs to the group of cardiac stimulants (ATC-Code: CO1 CA24).

2. Clinical Pharmacology

The actions of epinephrine resemble the effects of stimulation of adrenergic nerves. To a variable degree it acts on both alpha and beta receptor sites of sympathetic effector cells. Its most prominent actions are on the beta receptors of the heart, vascular and other smooth muscle. When given by rapid intravenous injection, it produces a rapid rise in blood pressure, mainly systolic, by (i) direct stimulation of cardiac muscle which increases the strength of ventricular contraction, (ii) increasing the heart rate and (iii) constriction of the arterioles in the skin, mucosa and splanchnic areas of the circulation. When given by slow intravenous injection epinephrine usually produces only a moderate rise in systolic and a fall in diastolic pressure. Although some increase in pulse pressure occurs, there is usually no great elevation in mean blood pressure. Accordingly, the compensatory reflex mechanisms that come into play with a pronounced increase in blood pressure do not antagonize the direct cardiac actions of epinephrine as much as with catecholamines that have a predominant action on alpha receptors.

Total peripheral resistance decreases by action of epinephrine on beta receptors of the skeletal muscle vasculature and blood flow is thereby enhanced. Usually this vasodilator effect of the drug on the circulation predominates so that the modest rise in systolic pressure which follows slow injection or absorption is mainly the result of direct cardiac stimulation and increase in cardiac output. In some instances peripheral resistance is not altered or may even rise owing to a greater ratio of alpha to beta activity in different vascular areas. Epinephrine relaxes the smooth muscles of the bronchi and iris and is a physiologic antagonist of histamine. The drug also produces an increase in blood sugar and glycogenolysis in the liver. Intravenous injection produces an immediate and intensified response.

Pharmacokinetics

As a result of enzymatic degradation in the gut and first pass metabolism in the liver, adrenaline is almost totally inactive when given orally. Systemic absorption can occur after topical application for example of eye drops. Adrenaline acts rapidly after IM or subcutaneous (SC) injection; the latter route is, however, sometimes considered to be slower and therefore less reliable in emergency use. Although absorption is slowed by vasoconstriction it can be hastened by massaging the site.

Onset of action within 2 minutes after IV or intraosseous (IO) administration. Onset of action within 5-10 minutes after IM administration. Duration of effect may range from 3-5 minutes intravascularly to upwards of 30 minutes intramuscularly.

Most adrenaline that is either injected or released into the circulation from the adrenal medulla, is very rapidly inactivated by processes that include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues. The half life of circulating adrenaline is only about 1 minute. One of the enzymes responsible for the chemical inactivation of adrenaline is catechol-O-methyltransferase (COMT), the other is monoamine oxidase (MAO). In general, adrenaline is methylatyed to metanephrine by COMT followed by oxidative de-amination by MAO and eventual conversion to 4-hydroxy-3methoxymandelic acid (formerly termed vanyllilmandelic acid (VMA), or oxidatively de-aminated by MAO and converted to 3,4-dihydroxy mandelic acid which in turn is methylated by COMT, once again to 4-hydroxy-3-methoxymandelic acid; the metabolites are excreted in the urine mainly as glucoronide and ethereal sulphate conjugates.

The ability of COMT is to effect the introduction of a methyl group in the chemical inactivation of adrenaline and similar catecholamines (in particular noradrenaline). It means that the termination of the pharmacological response is not simply dependent on MAO. In its role of neurotransmitter intra - neuronal catecholamine is, however, enzymatically regulated by MAO.

Epinephrine (adrenaline) crosses the placenta to enter the foetal circulation.

Therapeutic Uses

Epinephrine can activate all four subtypes of adrenergic receptors. As a consequence, the drug can produce a broad spectrum of beneficial sympathomimetic effects:
• Because it can cause alpha1-mediated vasoconstriction, epinephrine is used to:
(i) delay absorption of local anaesthetics,
(ii) control superficial bleeding, and
(iii) elevate blood pressure.
(iv) in the past, epinephrine-induced vasoconstriction was also used for nasal decongestion.

• Activation of alpha1 receptors on the iris can be used to produce mydriasis during ophthalmologic procedures.*

• Because it can activate beta1 receptors, epinephrine is used to:
(i) overcome atrioventricular (AV) heart block and (ii) restore cardiac function in patients experiencing cardiac arrest caused by asystole.

• Activation of beta-2 receptors in the lung promotes bronchodilatation, which can be useful in patients with asthma (although other drugs are nowadays preferred).

• Because it can activate a combination of alpha and beta receptors, epinephrine is the treatment of choice for anaphylactic shock.

The major effects of epinephrine (adrenaline) are dose related and include:

- Increased speed and force of cardiac contraction with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with high doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha receptors increases peripheral resistance.

- Increased blood flow to skeletal muscle (reduced with higher doses; reduced blood flow in the kidneys, mucosa and skin; little direct effect on cerebral blood flow.

- Relaxation of bronchial smooth muscle

- Hyperglycaemia and markedly increased oxygen consumption due to metabolic effects.

Epinephrine injection is an important life-saving drug and is used in advanced cardiac life support and in anaphylaxis in adults and children. It was used in the emergency treatment of acute asthma but more selective agents e.g. salbutamol, which has fewer effects on the heart have become available since the 1970s. Epinephrine has also been used administered by nebulisation in severe croup. Other uses include infiltration of the skin and other tissues in a diluted solution to create a bloodless field in surgery and to control minor bleeding from skin and mucous membranes during ENT surgery.

3. Discussion on clinical aspects and conclusion

A total of 11 medically-confirmed unsolicited cases of overdose were reported. All these cases come from literature.

Based on these data, a safety signal was identified in paediatric population because of the relatively frequent occurrence of epinephrine injection over dosage.

Rapporteur`s comments:

Basing on the information submitted from the MAH`s Global Pharmacovigilance Database:

Among the solicited cases there were three serious adverse events of two cases of Stevens-Johnson syndrome and one case of erythema multiforme in patients who had numerous concomitant medications.

Among the 35 unsolicited cases 27 came from the literature and 8 were sent directly to the MAH and involved 153 reactions. This population included the frequently reported reactions of accidental overdose 7/153 (4.6%) and overdose 4/153 (2.6%). Together they make up 11/153 (14.9%) of reactions reported. This high frequency of overdose of epinephrine in children, which included one fatality, is a matter of some concern.

Overall epinephrine is considered effective and safe in children if used for the authorised indications at the correct recommended doses for children. Pharmacological dose dependent effects are to be reckoned with.

From the safety information provided and other data it results that over dosage and accidental over dosage are fairly frequent events. These iatrogenic errors resulted from underlying confusion by physicians about proper dosing of epinephrine for anaphylaxis. The risk of error was amplified by the need for rapid decision making in critically ill anaphylactic patients. This suggests that clear and unmistakable information with regard to paediatric dosage of intramuscular epinephrine should be highlighted as a table in the SmPC and this should be reflected in the patient leaflet (PL) so that the user will be made aware of the importance of correct dosage in children. The information should stand out from the complicated instructions for IV use in which the current epinephrine IM paediatric dose tends to be less prominent.

Multiple case reports of epinephrine dosing errors in patients with anaphylaxis have been published. These reports describe inadvertent intravenous administration of 1:1000 solution or intravenous administration of the higher cardiac arrest dose epinephrine. The smaller volume of medication and intramuscular administration of the 1:1000 concentration are less familiar.

The reasons for dosing errors are likely multi-factorial. Besides the familiarity with cardiac arrest dosing and intravenous administration, the 1:1000 concentration is less familiar. The authors of one concept paper published in *Annals of Emergency Medicine* recommend that Emergency Departments (EDs) add easy-to-read labels to epinephrine syringes to distinguish intramuscular and intravenous preparations and avoid inadvertent intravenous administration of concentrated epinephrine. Another problem is that the concentration is expressed as a ratio (1:1000) and providers are more accustomed to mass concentrations (1 mg/ml).

With regard to the 1:1000 epinephrine formulation it has to be diluted 1 in 10 before intravenous use. This may not be difficult in the hospital setting but may be very challenging for the doctor treating an emergency in the community.

In order to avoid mistakes in dosage in children, because of the large variety of available epinephrine formulations, it is considered that for safety reasons, in addition from dosage in mg/kg, for better guidance of the occasional or infrequent user of the 1mg/ml epinephrine injection 1:1000, the Summary of Product Characteristics (SmPC) and the package leaflet (PL) should contain the recommended doses for children in a table with doses in both weight and volume together with advice to use a suitable syringe for measuring a small volume.

Because of the small volumes of intramuscular epinephrine injection required in children and because of the potential for dosage errors it is therefore recommended that all SmPCs and patient leaflets/package inserts, an additional the generally accepted dosage information of 0.01 mg/kg body weight, should contain a table indicating the appropriate weight and volume of epinephrine according to age. This will contribute to greater awareness about appropriate paediatric epinephrine IM dosage. It will also ensure adequate treatment and help diminish dosage errors.

Because of the wide range of several possible conditions requiring epinephrine treatment for convenience the clinical overview of efficacy of epinephrine can be discussed according to the following indications as they appear in the SmPCs of Epinephrine1mg/ml injection:

Cardiopulmonary resuscitations
Anaphylaxis
Septic shock (not an approved indication in children)
Local haemostasis

3. 1.Cardiopulmonary resuscitation

When the heart is no longer effectively pumping blood in the body there is cardiopulmonary failure (CPF). In cardiopulmonary failure oxygen is no longer effectively delivered to the vital organs and this leads to collapse and cardiac arrest. The causes of cardiac arrest (CA) in infants and children differ characteristically from the causes in adults in whom there is likely to be underlying ischemia, due to coronary disease, leading to myocardial infarction or cardiac arrhythmia which may precede cardiac arrest.

Outcomes following CAs occurring in the community are much worse than those occurring in hospital. Survival to time of hospital discharge occurs < 10% of these children and many have severe neurological sequelae. The two conditions that have the worst outcome are traumatic arrests and sudden infant death syndrome (SIDS). Traumatic cardiac arrests result from either severe prolonged hypoxic episodes or exsanguinations. SIDS subjects are often long dead before resuscitation is attempted. More often than not in CA occurring in the community incidents of cardiac arrest cardiopulmonary resuscitation (CPR) and advanced cardiovascular life support (ACLS) are typically applied after prolonged periods of profound hypoxia and hypo-perfusion of vital organs.

In the neonatal situation CPF and cardiac arrest (CA) occur in the setting of neonatal asphyxia of the transition from the foetal circulation in utero to post natal spontaneous respiration.

The main causes of CPF and CA in infants and older children are broadly due to:

1. Trauma due to violent physical injury in accidents and child abuse causing wounds an damage to vital organs and blood loss which both can lead to blood loss which together with intense pain can lead to shock which in turn if not promptly treated can lead to CV collapse.
2. This can occur by ingestion, inhalation or skin contact. Poisoning can result in interference with pulmonary and tissue respiration, loss of consciousness, seizures, CVF and death.
3. Respiratory disorders; these include laryngeal obstruction and severe bronchspasm in unrelieved acute severe asthma, smoke inhalation, near drowning, severe pneumonia and sudden infant death syndrome.
4. Severe infections by invasive pathogens with severe fluid loss and multiple organ damage as in septic shock in severe inflammatory response syndrome (SIRS) and toxic shock syndrome (TSS).

Children in general have a healthy heart to begin with. Prevention of CPF and CA has a very important role. Increased awareness of situations and prompt intervention in situations which lead to CPF have a very important role.

Cardiac arrest is initially managed by Basic Life Support which ensures a free airway, ventilation, and circulation by chest compression as first aid until arrival of until management is taken over by personnel trained and equipped to administer advanced cardiovascular life support (ACLS). If ventilation and chest compression do not restore spontaneous circulation and respirations then ACLS methods and pharmacological agents are required. The ACLS team can incubate the patient, provide venous access, correct hypovolaemia and carry out ECG monitoring and defibrillation if necessary.

Apart from these measures the ACLS team will administer vaso-active drugs by continuous IV infusion to stimulate and maintain adequate cardiac function. Among the pharmacological agents used epinephrine is a first line agent which has a very important role. The α-adrenergic action increases vascular resistance increasing diastolic blood pressure which in turn increases coronary perfusion pressure and blood flow increasing the likelihood of return to spontaneous circulation (ROSC) Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of the blood flow to the brain .The β-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the muscular bed and in the bronchi. Epinephrine also increases the vigour and intensity of ventricular fibrillation, increasing the likelihood of success of defibrillation.

High dose epinephrine can worsen a patient's post resuscitation haemodynamic condition with increased myocardial oxygen demand, ventricular ectopia and hypertension. A randomized blinded controlled trial of high dose epinephrine versus standard dose did not show any benefit of high-dose epinephrine rescue therapy for in-hospital cardiac arrest in children after failure of an initial standard dose of epinephrine. The data suggest that high-dose therapy may be worse than standard-dose therapy.

The standard recommended dose of epinephrine recommended by the American Heart Association (AHA) guidelines for paediatric resuscitation is:

IV/IO: 0.01mL/kg 1:10000. Maximum 1mg. May be repeated every 3-5 minutes
Endotracheal (ET): 0.1mL/kg of 1:1000. Max. 2.5 mg.

N.B.: **Epinephrine1:1000 injection MUST be diluted to 1:10000 for CPR.**

Higher doses of 100 - 200mcg/kg have been used in second and subsequent doses. However, as with adults, the use of higher doses is not routinely recommended and both retrospective and prospective studies have found no improvement in outcome.

According to Section 6 of the European Resuscitation Council Guidelines for Resuscitation 2010, regarding epinephrine in paediatric life support gives the following evidence-based information:

"The recommended IV / IO dose of adrenaline in children for the first and subsequent doses is 10 mcg/kg. The maximum single dose is 1mg. If needed, give further doses of adrenaline every 3-5 minutes. Intra tracheal adrenaline is no longer recommended, but if this route is used the dose is ten times this (100mcg/kg). The use of higher doses of adrenaline (epinephrine) via the IV or IO route is not recommended as it does not improve survival or neurological outcome after cardiopulmonary arrest".

Rapporteur`s comment:

Epinephrine has a vital role in the management of cardio-pulmonary resuscitation in the context of ACLS management after CPR. Because of its powerful pharmacodynamic effects great attention is needed in its administration as an **IV** infusion the rate of which can be monitored and controlled so that the dose can be titrated at the correct dilution (1:10000), with the correct dose and at a safe rate of administration according to the protocols in the emergency department, neonatal and paediatric intensive care unit.

High-dose epinephrine (HDE) rescue therapy in children with in-hospital cardiac arrest does not improve the rate of survival at 24 hours. Among children with asphyxia-precipitated cardiac arrest HDE appears to be harmful.

The **IM** route is generally preferred in the initial treatment of anaphylaxis, the **IV** route is generally more appropriate for CPR in the ICU setting. Epinephrine injection 1:1000 is not suitable for IV use. If the epinephrine1:10000 solution for injection is not available, epinephrine solution for injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of epinephrine must be used with extreme caution.

The ERC guidelines suggest that:
"*Intravenous adrenaline should be used only by those experienced in the use of titration of vasopressors in their normal clinical practice (e.g., anaesthetists, emergency physicians and intensive care doctors)."*

3.2 Anaphylaxis

The World Allergy Organisation defines anaphylaxis as is an acute, potentially life-threatening hypersensitivity reaction, involving the release of mediators from mast cells, basophils and recruited inflammatory cells. Anaphylaxis is defined by a number of signs and symptoms, alone or in combination, which occur within minutes, or up to a few hours, after exposure to a provoking agent. It can be mild, moderate to severe, or severe.

Most cases are mild but any anaphylaxis has the potential to become life-threatening.

Anaphylaxis develops rapidly, usually reaching peak severity within 5 to 30 minutes, and may, rarely, last for several days.

Infants can present a special challenge, as the hallmark symptoms and signs of anaphylaxis may be mistaken as normal findings. These include drooling, vomiting or diarrhoea, scratching, and drowsiness. The clinical manifestations of anaphylaxis are broad, as a result of it being a systemic response to an external agent. Among infants and children, there are often respiratory and cutaneous findings. There also can be subtle signs and symptoms, which can often be missed or the findings misinterpreted as normal for developmental age. The incidence of anaphylaxis has increased globally among children presenting with allergic reactions. Early recognition of the signs and symptoms is crucial to effective diagnosis and treatment. This is particularly true among infants 13 months of age or younger who are nonverbal and may have subtle signs and symptoms of a life-threatening reaction to allergens. The purpose of this article is to highlight the differential clinical presentations of young children with anaphylaxis.

The most common causes of anaphylaxis are insect stings, medicinal products, latex, nuts, foods in particular shellfish, fish, milk, eggs and wheat.

The initial manifestation of anaphylaxis may be loss of consciousness. Patients often describe "a sense of doom." In this instance, the symptoms and signs of anaphylaxis are isolated to one organ system, but since anaphylaxis is a systemic event, in the vast majority of subjects two or more systems are involved:

Gastro-intestinal: Abdominal pain, hyperperistalsis with faecal urgency or incontinence, nausea, vomiting, diarrhoea.

Oral: Pruritus of lips, tongue and palate, oedema of lips and tongue.

Respiratory: Upper airway obstruction from angioedema of the tongue, oropharynx or larynx; bronchospasm, chest tightness, cough, wheezing; rhinitis, sneezing, congestion, rhinorrhea.

Cutaneous: Diffuse erythema, flushing, urticaria, pruritus, angioedema.

Cardiovascular: Faintness, hypotension, arrhythmias, hypovolemic shock, syncope, chest pain.

Ocular: Periorbital oedema, erythema, conjunctival erythema, tearing.

Genito-urinary: Uterine cramps, urinary urgency or incontinence.

Severe initial symptoms develop rapidly, reaching peak severity within 3-30 minutes. There may occasionally be a quiescent period of 1–8 hours before the development of a second reaction (a bi-phasic response). Protracted anaphylaxis may occur, with symptoms persisting for days. Death may occur within minutes but rarely has been reported to occur days to weeks after the initial anaphylactic event.

Besides any attention needed to ensure airway, breathing and circulation, prompt administration of epinephrine is promptly indicated to reverse the manifestations of anaphylaxis. This is the urgent initial management.

The early use of epinephrine in vitro inhibits the release of PAF in a time-dependent manner, giving support to the use of this medication with the first signs and symptoms of anaphylaxis. The usual dosage of epinephrine for adults is 0.3-0.5 mg of a 1:1000 w/v solution given intramuscularly every 10-20 minutes or as necessary. The dose for children is 0.01 mg/kg to a maximum of 0.3 mg intramuscularly every 5-30 minutes as necessary. Lower doses, e.g., 0.1 mg to 0.2 mg administered intramuscularly as necessary, are usually adequate to treat mild anaphylaxis, often associated with skin testing or immunotherapy. Epinephrine should be given early in the course of the reaction and the dose titrated to the clinical response. For severe hypotension, 1 cc of a 1:10000 w/v dilution of epinephrine given slowly intravenously is indicated. The patient's response determines the rate of infusion.

Epinephrine is one of the listed WHO essential medicines for children for the treatment of anaphylaxis. There is a consensus of the need for prompt administration of IM epinephrine injection in the initial treatment of anaphylaxis. The WAO guidelines recommend to have a protocol; remove the trigger, if relevant, assess rapidly, promptly and simultaneously call for help, inject epinephrine IM, repeat in 5-15 min, position the patient supine (semi-reclining if dyspnoeic or vomiting) with lower extremities elevated

According to AAAAI/JCAAI two Guidelines: epinephrine IM is the initial medication of choice; repeat in 5 minutes; have a protocol; remove exposure to the trigger; position the patient supine (semi-reclining if dyspnoeic or vomiting) with lower extremities elevated; call for help.

The intramuscular (IM) route is the best for most individuals who have to give epinephrine to treat an anaphylactic reaction. Monitor the patient as soon as possible (pulse, blood pressure, ECG, pulse oximetry). This will help monitor the response to epinephrine. The IM route has several benefits:

- There is a greater margin of safety.
- It does not require intravenous access.
- The IM route is easier to learn.

The ERC guidelines suggest that:
"*Intravenous adrenaline should be used only by those experienced in the use of titration of vasopressors in their normal clinical practice (e.g., anaesthetists, emergency physicians and intensive care doctors).*"

The best site for IM injection is the anterolateral aspect of the middle third of the thigh.

Epinephrine IM dose – children

Regarding the use of epinephrine (adrenaline) in children in paediatric anaphylaxis, Section 8 of the European resuscitation Council (ERC) guidelines for Resuscitation 2010 (Nolan *et al. (2010)* Resuscitation 81: 1219-1276 states:

"The evidence for the recommended doses is weak. Doses are based on what is considered to be safe and practical to draw up and inject in an emergency. (The equivalent volume of 1:1000 adrenaline (epinephrine) is shown in brackets).

The recommended doses are as follows:

> 12 years: 500 micrograms IM (0.5 ml) i.e. same as adult dose
300 micrograms (0.3 ml) if child is small or prepubertal
> 6 – 12 years: 300 micrograms IM (0.3 ml)
> 6 months – 6 years: 150 micrograms IM (0.15 ml)
< 6 months: 150 micrograms IM (0.15 ml)

IV adrenaline is best reserved those experienced in the use and titration of vasopressors in their normal clinical practice (e.g., anaesthetists, emergency physicians, intensive care doctors).

In a study reported by Simons et al. it was reported that most parents were unable to draw up an infant epinephrine dose rapidly or accurately. Most health care professionals drew up the dose rapidly; however, their accuracy was compromised by inherent variations of epinephrine concentrations in the ampoules (United States Pharmacopeia compendial limits, 90% to 115%) and the inherent difficulty of measuring small volumes (<0.1 ml) of epinephrine. User-friendly premeasured epinephrine doses suitable for infants should be developed.

Further management may involve treatment with beta-2 agonists, steroids, antihistamines or referral to the emergency department for intensive care depending on response and severity. In any case further evaluation by an immunologist is needed with a view to establish the cause, avoidance measures, provision of information and training on future avoidance and advice carrying a personal pre-filled type syringe with age/weight appropriate dose of epinephrine.

Rapporteur`s comment:

The occurrence of anaphylaxis in children can be a very traumatic event for the child, stressful for the parents and an often challenging event for the medical attendant. Epinephrine injection is a powerful medication with a potential for error because of the small volume required for injection in children. Children are further at risk from errors in weight–based calculations and confusion over drug concentration expression, which may result in dangerous overdose.

The dose recommended for paediatric anaphylaxis is 0.01mg/kg (0.01ml/kg) of 1:1000 epinephrine injection with a maximum of 0.3mg administered IM to the vastus lateralis in the mid outer thigh and may be repeated every 5 to 15 minutes for recurrent symptoms.

During an emergency one cannot expect all health care practitioners to be familiar with percent or ratio expressions of concentrations or to be adept at calculating doses for drugs with concentrations expressed in this manner. Calculating the correct epinephrine dose in the heat of a paediatric emergency may be very challenging.

In order to reduce the possibility of error, especially for those who are not familiar with the use of epinephrine, besides the dose in mg/kg an additional table showing the volume of the epinephrine injection 1:1000 injection is recommended to be included in all SmPCs and PLs and/or package inserts of the injection where the recommended doses are currently in practice. This is a safe strategy to help ensure greater awareness of the appropriate dose in children.

Children: The following doses of epinephrine1:1000 are recommended:

Age	**Dose**
Over 12 years	500 micrograms (0.5ml)
6 – 12 years	300 micrograms (0.3l) if child is small or prepubertal
6 months - 6 years	0.15 mg IM (0.15ml 1:1000 solution)
Under 6 months	0.01mg/kg IM (0.01ml/kg 1:1000 solution)

If necessary, these doses may be repeated several times at 5 – 15 minutes intervals according to blood pressure, pulse and respiratory function. A small volume syringe should be used for accurate measurement of the dose.

Furthermore the IM route should be the recommended mode of administration in initial treatment of paediatric anaphylaxis.

3.3 Septic shock

This is not an approved indication for epinephrine injection 1:1000 in children.
Toxic shock syndrome (TSS) is an acute toxin mediated illness caused most commonly by toxin producing invasive strains of *Staphylococcus aureus* and *Streptococcus pyogenes* and other invasive micro-organisms. The onset may be rapid and even fulminant. Mortality varies from 20 to 50%.

Comprehensive information about this clinical picture of invasive infections with shock and system failure, which includes TSS, and of its management may be found under the heading of paediatric Systemic Inflammatory Response Syndrome (SIRS) which might require treatment with vasopressors. SIRS has a wider connotation than toxic shock syndrome (TSS). The definition has been adapted from adult (SIRS).

The child with septic shock looks very ill and shocked with decreased awareness and mental state, may be irritable, with diarrhoea and /or vomiting, fever, possibly a rash (commonly non-specific diffuse macula-papular) a cold extremities, delayed capillary permeability of the skin, weak rapid peripheral pulses, hypotension, respiratory distress, hepatic and renal involvement with low urine output. Thrombocytopenia and coagulopathy may be late development

The diagnosis is a clinical one. Favourable outcome depends on early diagnosis and prompt initiation of treatment in intensive care. The treatment regimen for staphylococcal toxic shock syndrome (TSS) includes the following:

The treatment regimen includes administration of normal saline or colloids. Intractable hypotension that results from diffuse capillary leaking may require large amounts of these fluids. Albumin replacement may be necessary in patients in whom albumin levels drop lower than 2 g/dl. Vasopressor / inotrope infusion should be performed as necessary. Aggressive supportive care in an ICU is needed.

Treatment

Consensus guidelines exist for the management of infants and children with septic shock. There is some evidence that adherence to these recommendations has improved survival. Management can be broadly divided into two main phases:

ABCs: During the first hour of resuscitation, fluid and inotropic drug therapy is directed towards maintaining goals of age appropriate heart rate, blood pressure, and a normal CRT $\geq$ 2 seconds Oxygenation and ventilation should be supported as appropriate.

Stabilization: beyond the first hour, management should move to an intensive care setting for further haemodynamic support and goal directed therapy. Treatment targets include normal perfusion pressure for age, ScvO2 > 70%, and Cardiac Index (CI) 3.3-6 L/min.

Vasopressors — Children who have not improved after 60 ml/kg of isotonic crystalloid should receive vasoactive therapy in addition to continued fluid administration. The following vasoactive infusions should be considered:

- Low dose dopamine (2 to 5 mcg/kg/min) for children who are normotensive
- Beta adrenergic dose of dopamine (5 to 10 mcg/kg/min) or norepinephrine for those who are hypotensive and vasodilated
- Epinephrine for children who are hypotensive and vasoconstricted despite maximum beta adrenergic doses of dopamine and/or norepinephrine

If adequate resuscitation end-points are not reached by fluid resuscitation alone- a so-called state of “fluid refractory shock”—the patient will need vaso/active/inotropic agents. Dopamine remains the most common first choice for patients with fluid refractory shock. Dopamine possesses dose dependent agonistic effects on dopaminergic and adrenergic (α and β) receptors. If the haemodynamic resuscitation end-points are not achieved with adequate fluid and clinicians are increasingly choosing low-dose epinephrine to achieve adrenergic-mediated inotropic support as a first line therapy for fluid refractory shock (see below). When the hemodynamic resuscitation end-points are not achieved with adequate fluid and dopamine/low-dose epinephrine administration, further management of this so called state of “fluid-refractory, dopamine-resistant shock” is indicated by the clinical context.

Epinephrine/Norepinephrine The decision of which agent to add in the setting of fluid refractory, dopamine-resistant shock is based on the underlying cause of cardiovascular compromise and the presenting hemodynamic profile. In the paediatric population it more common to have low cardiac output with increased systemic vascular resistance as compared to adults who most often present with high cardiac output and low systemic vascular resistance. As a result, low-dose epinephrine is chosen as the second line inotropic agent most often. Epinephrine provides inotropic support via alpha1 receptor stimulation and modest vasodilatation via beta 2 receptor stimulation when administered at low concentrations (0.02- 0.3 mg/kg/min).

Rapporteur`s comments:
This is not an approved indication for epinephrine injection 1:1000 in children. Children with such serious infections are treated in an intensive care setting and any vasoactive / inotropic agents would be given intravenously (IV) at a controlled rate according to response. Any epinephrine injection 1:1000 would have to be suitably diluted to 1 in 10000 so that it can be given by IV according to established protocols.

It would appear that in childhood TSS / SIRS in fluid refractory shock vasoactive or inotropic agents are needed. Dopamine remains the most common first choice for patients with fluid refractory shock in children. Dopamine possesses dose dependent agonistic effects on dopaminergic and adrenergic (α and β) receptors. Low-dose epinephrine is chosen as the second line inotropic agent if fluid refractory, dopamine-resistant shock persists.

3.4 Local haemostasis

Epinephrine is used in many surgical procedures in the nose, throat and larynx to shrink the mucosa and improve visualization by limiting haemorrhage. Some orthopaedic surgeons use infiltration with a dilute solution of epinephrine to ensure a bloodless operating field. Sufficient amounts of epinephrine may be absorbed to interact with general anaesthetics.

In local anaesthesia, rapid absorption of drugs used results in low anaesthetic effects or short duration of action. The local alpha-agonist effects of epinephrine induce vasoconstriction. Therefore, adding epinephrine to local anaesthetics has the potential to extend duration of anaesthesia, improve relief of pain, decrease surgical bleeding, lessen mucosal congestion, keep clear sight on the vascularity areas, and decrease systemic toxicity of the anaesthetic agent.

Accordingly epinephrine is commonly administered as an adjuvant of local anaesthesia in many surgical procedures, mainly in the Ear Nose Throat (ENT) setting and dental surgery. Indeed, epinephrine may be added to anaesthetic solutions in local infiltrations for general surgery in adults and children to prolong duration of anaesthesia, e.g. for repair of minor lacerations or skin biopsies.

Rapporteur`s comment:

This seems to be a long established practice used to control haemorrhage in ENT. It is important for the surgeon to inform the anaesthetist of the use of epinephrine because of the possibility of systemic absorption of topically applied epinephrine and interaction with general anaesthetics such as halothane.

V. MEMBER STATES Overall Conclusion AND RECOMMENDATION

Overall conclusion

It is recommended by the Rapporteur that apart from the generally accepted dosage of epinephrine 0.01mg/kg an additional dosage table according to age may be included in the Member States where the recommended doses are currently in practice. Some MSs may not to wish to include this additional dosage table.

The benefit/risk of epinephrine in children continues to be safe when used in the correct dosage for the right indication.

The MAH is requested to submit a type IB variation within 60 days from the finalisation of this worksharing procedure in order to be able to include the recommendation in the Product Information.

In addition to the generally accepted dosage of 0.01mg/kg body weight SmPCs may have an additional table of recommended paediatric doses as indicated above in Section **4.2 Posology and mode of administration** of the SmPC.

Further in the SmPC under Section **4.4 Special warnings and precautions for use** it is recommended that there should be the following cautionary statement:

"The IM route is generally preferred in the initial treatment of anaphylaxis, the IV route is generally more appropriate for CPR in the ICU setting. Epinephrine injection 1:1000 (1mg/ml) is not suitable for IV use. If the epinephrine1:10000 (0.1mg/ml) injection is not available, epinephrine injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of epinephrine must be used with extreme caution."

Recommendation

Type IB variation to be requested from the MAH within 60 days in line with Section I. Executive Summary and Summary of outcome.

X **Change:** new safety data from medical literature in section 4.2 and 4.4 of the SmPC of Epinephrine(adrenaline) concerns the 1mg/ml (1:1000) injection products only.

Section 4.2 of the SmPC: An additional table with recommended intramuscular (**IM**) paediatric doses (see below) for anaphylaxis may be included in the Member States where the recommended doses are currently in practice.

Age	Dose of epinephrine1mg/ml (1:1000 solution)
Over 12 years	0.5 mg IM (0.5ml 1:1000 solution)
6 - 12 years	0.3 mg IM (0.3ml 1:1000 solution)
6 months - 6 years	0.15 mg IM (0.15ml 1:1000 solution)
Under 6 months *	0.01mg/kg IM (0.01ml/kg 1:1000 solution)

If necessary, these doses may be repeated several times at 5 – 15 minutes intervals according to blood pressure, pulse and respiratory function.
A small volume syringe should be used.

Section 4.4 of the SmPC to add the following:

The IM route is generally preferred in the initial treatment of anaphylaxis, the IV route is generally more appropriate in the Intensive Care Unit (ICU) or Emergency Department (ED) setting. Epinephrine injection 1:1000 (1mg/ml) is not suitable for IV use. If the epinephrine1:10000 (0.1mg/ml) injection is not available, epinephrine injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of epinephrine must be used with extreme caution and is best reserved for specialists familiar with IV use of epinephrine (adrenaline).

X Paediatric information clarified:

In **Section 4.2 and 4.4** of the SmPC: see above recommendations.

The MAH is requested to submit a type IB variation within 60 days from the finalisation of this worksharing procedure in order to be able to include the recommendation in the Product Information.

VI. List of Medicinal products and marketing authorisation holders involved

Invented name of the medicinal product(s):	Suprarenin ampoules (1mg/ml solution for injection) Suprarenin vial (1mg/ml solution for injection) Suprarenin 1mg/ml solution for injection
MAH (s):	1.) Sanofi-Aventis Deutschland GmbH D-65926 Frankfurt am Main Germany Postal address: Postfach 80 08 60 D-65908 Frankfurt am Main Germany 2.) sanofi-aventis GmbH Leonard-Bernstein-Straße 10 1220 Vienna Austria 3.) sanofi-aventis d.o.o., Dunajska cesta 151, Ljubljana Slovenija