LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Adrenalin Martindale Pharma
(adrenaline tartrate)

SE/H/1658/01/MR

This module reflects the scientific discussion for the approval of Adrenalin Martindale Pharma. Please note that the marketing authorisation was first approved with the name "Adrenalin Jacobsen Pharma" and therefore this name is used throughout the document. The procedure was finalised at 2014-02-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Jacobsen Pharma A/S has applied for a marketing authorisation for Adrenalin Jacobsen Pharma, 0,1 mg/ml, solution for injection. The application is submitted in accordance with Directive 2001/83/EC Article 10a, so called well-established use (WEU) application. For a WEU application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use.

In a WEU application, results of pre-clinical and clinical trials are replaced by detailed references to published scientific literature.

The active substance is adrenaline tartrate.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Adrenalin Jacobsen Pharma is presented in the form of a solution for injection containing 0.18 mg/ml of adrenaline tartrate which corresponds to 0.1 mg/ml of adrenaline. The excipients are sodium chloride, citric acid monohydrate, sodium citrate, sodium metabisulfite, hydrochloric acid and water for injections. The solution for injection is filled in glass ampoules.

II.2 Drug Substance

Adrenaline tartrate has a monograph in the Ph Eur.

Adrenaline tartrate is a white or greyish white, crystalline powder which is freely soluble in water and slightly soluble in ethanol. The structure of adrenaline tartrate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Adrenalin Jacobsen Pharma solution for injection is formulated using excipients described in the current Ph Eur. The drug product does not contain any excipients of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C.

III. NON-CLINICAL ASPECTS

The non-clinical part of the application was submitted as a bibliography. No new non-clinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

Adrenaline has been studied extensively in various non-clinical models and there is a long clinical experience with the substance.

Adrenaline is an endogenous substance not expected to pose any significant risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

This is a well established use application which is solely based on bibliographic data. Adrenaline is a well known active substance that has been extensively reviewed in the literature. After intravenous administration, adrenaline is rapidly inactivated in the body mostly by the enzymes COMT and MAO. Much of the dose of adrenaline is accounted for by excretion of metabolites in the urine. The plasma half-life of adrenaline is about 2.5 min.

Adrenaline Jacobsen Pharma is an aqueous solution for injection containing comparable excipients as other adrenaline products on the market. Hence, similar bioavailability as other adrenaline solutions for injections referred to in the literature is expected.

IV.2 Pharmacodynamics

Adrenaline has a number of effects which are dose related (Saeb-Parsy K, 1999):

It exerts positive cardiac inotropic and chronotropic effects which lead to an increase in cardiac output. The overall effect on the vasculature is vasoconstriction, with the exception of skeletal muscle vasculature where vasodilatation predominates due to a predominance of β2-adrenoceptors. Adrenaline thus causes a rise in systolic blood pressure, though diastolic blood pressure may actually fall due to a reduction in total peripheral resistance. These actions are exploited in the treatment of shock and cardiac arrest.

Adrenaline acts directly to relax bronchial smooth muscle which may relieve airway obstruction in allergic reactions. In addition, it is thought to inhibit the release of inflammatory mediators from cells as well as decreasing bronchial mucous secretion.
Adrenaline causes an increase in renin secretion which leads to increased salt and water retention.
Its vasoconstrictor properties prolong the action of local anaesthetics by preventing their systemic spread.
Adrenaline lowers intraocular pressure probably through both a reduction in the production of aqueous humour and an enhancement of its outflow.
Insulin secretion is decreased and glucagon secretion increased, thus mobilising energy reserves.

Cardiopulmonary Resuscitation
Adrenaline has an important role in advanced cardiac life support since, through its alpha agonist effects; it concentrates the blood around the vital organs, specifically the brain and the heart, by peripheral vasoconstriction. Adrenaline also strengthens cardiac contractions as it stimulates the cardiac muscle via its binding to β1 receptors. This further increases the amount of blood circulating to the vital organs, and also increases the chance of the heart returning to a normal rhythm (Martindale).

Acute Anaphylaxis
Anaphylaxis is usually a type 1 hypersensitivity reaction in which there is an IgE-mediated activation of mast cells and basophils, usually as a result of exposure to allergens such as drugs, foods and insect venom. A clinically identical reaction can, however, be provoked by a type II mechanism, as in blood transfusion reactions or a Type III mechanism, as in drug-induced serum sickness reactions; anaphylactoid reactions are similar but are caused by direct histamine release rather than hypersensitivity. Symptoms of anaphylaxis and anaphylactoid reactions include erythema, pruritus, urticaria and angioedema; respiratory obstruction may result from oedema of the larynx or epiglottis. Gastrointestinal disturbances, bronchospasm, hypotension and coma can occur in severe reactions (Martindale).

Anaphylaxis is a medical emergency and prompt treatment of laryngeal oedema, bronchospasm and hypotension is necessary.

Adrenaline has physiological benefits in the treatment of anaphylaxis: stimulation of α adrenoceptors increases peripheral vascular resistance thus improving blood pressure and coronary perfusion, reversing peripheral vasodilation, and decreasing angioedema. Stimulation of β1 adrenoceptors has both positive inotropic and chronotropic cardiac effects. Stimulation of β2-receptors causes increased bronchodilation as well as increasing intracellular cyclic adenosine monophosphate production in mast cells and basophils, reducing release of inflammatory mediators (McLean-Tooke A, 2003; Simons K, 2010).

IV.3 Clinical efficacy

Cardiopulmonary resuscitation
Although historically and currently recommended for use in cardiac arrest, adrenaline, either in high or low dosages, has never been shown in a placebo-controlled trial to improve survival to hospital discharge. Due to its lack of proven efficacy new vasopressors for cardiac arrest have been investigated:

Stiell et al. (2001) performed a prospective, triple-blind, randomized, and controlled trial evaluating vasopressin in hospitalized patients with cardiac arrest. Patients experiencing VF,

PEA, or asystole (n = 200) were randomized to receive a singe i.v. dose of either adrenaline 1 mg or vasopressin 40 units. Successful resuscitation was achieved in 39% of the vasopressin-treated group and 35% of the adrenaline-treated group; there was no significant difference in success rates between the two groups. Rates of survival to hospital discharge also did not significantly differ between the vasopressin-treated group (12%) and the adrenaline-treated group (14%).

Wenzel et al. (2004) conducted a prospective, double-blind, randomized, and controlled trial of 1219 patients with out-of hospital VF, PEA, or asystolic cardiac arrest. Patients were randomly assigned to receive adrenaline 1 mg i.v. or vasopressin 40 units i.v. If spontaneous circulation was not restored within three minutes, a second dose of the same agent was administered. Overall, there was no significant difference in survival to hospital admission (36.3% with vasopressin versus 31.2% with adrenaline) or survival to hospital discharge (9.9% for both groups). There was also no difference in either endpoint in the subgroup populations of VF and PEA; however, a difference was found in patients with asystole. Asystolic patients treated with vasopressin had a survival to hospital admission rate of 29.0%, compared with 20.3% in patients treated with adrenaline ($p = 0.02$). There was also a significant difference in survival to hospital discharge, which occurred in 4.7% and 1.5% in the vasopressin- and adrenaline-treated groups, respectively ($p = 0.04$).

Gueugniaud et al. (2008) conducted a prospective, double-blind, randomized controlled trial of 2894 patients with out-of hospital VF, PEA, or asystolic cardiac arrest. Patients were assigned to receive adrenaline 1 mg i.v. and vasopressin 40 units i.v. or adrenaline 1 mg i.v. alone. If spontaneous circulation was not restored within three minutes, a second dose of the same regimen was administered. Overall, there was no significant difference between the combination therapy and the group receiving adrenaline alone in survival to hospital admission (20.7% versus 21.3%, respectively) or survival to hospital discharge (1.7% versus 2.3%, respectively). In this study, 83% of the patient population was enrolled after an asystolic arrest, failing to confirm the suggestion by Wenzel et al. that vasopressin may be beneficial in this patient population.

Although there is evidence that vasopressors (adrenaline or vasopressin) may improve ROSC and short-term survival, there is insufficient evidence to suggest that vasopressors improve survival to discharge and neurological outcome. There is also insufficient evidence to suggest the optimal dosage of any vasopressor in the treatment of adult cardiac arrest. However, given the observed benefit in short-term outcomes, either adrenaline or vasopressin may be considered as first-line agents in cardiac arrest.

Justification for dose in Cardiopulmonary Resuscitation

The optimum dose of adrenaline has been a topic of considerable controversy. The original recommended dose of adrenaline in advanced cardiac life support (ACLS) was 0.5–1 mg every 5 minutes. However, continued low survival rates in the late 1980s and anecdotal observations in case reports of success with use of higher doses suggested the need to re-evaluate dosing recommendations. The effectiveness of a higher dose of adrenaline, greater than 5 mg or 0.1 mg/kg, was compared with a standard dose of 1 mg in both the in-hospital and out-of-hospital settings (Stiell I, 1992; Brown C, 1992). Higher adrenaline doses appeared to be associated in some trials with a slight increase in rates of resuscitation, but at a cost of a higher frequency of post resuscitation complications mediated by β-adrenergic effects, including increased myocardial oxygen consumption and metabolic demand that may predispose patients with underlying myocardial ischemia to cardiac dysfunction and arrhythmias (Stiell I, 1992). Higher adrenaline doses may increase the frequency of adverse neurologic outcomes, with longer duration of hospitalization. With the exception of selected observations in patients with

asystole, pooled odds ratios of survival to hospital discharge in meta-analyses of trials comparing standard-dose with high-dose adrenaline show a trend favouring the standard 1-mg dose (Vandycke C, 2000). Although the optimum dose or approach for adrenaline in pulseless situations (ventricular fibrillation, asystole, PEA) has not been clearly established, a dose of 1 mg is usually recommended (Vandycke C, 2000, ERC, 2010)

Acute Anaphylaxis

Adrenaline is the most important drug for the treatment of an anaphylactic reaction (RC (UK), 1999; Working Group of the Resuscitation Council (UK), 2008). No randomized controlled trials that meet optimal standards have been published for any medication used in the treatment of acute anaphylaxis; however, the evidence base for adrenaline injection in anaphylaxis is stronger than the evidence base for use of H1-antihistamines, H2-antihistamines, or glucocorticoids in the initial treatment of this disease (Sheikh A, 2009; Choo K, 2010).

Results of a 2009 Cochrane systematic review of adrenaline for the treatment of anaphylaxis failed to uncover any evidence from prospective, randomized or quasi-randomized trials on the effectiveness of adrenaline for the emergency management of anaphylaxis. However, given the relative infrequency of the condition, the speed of onset, the often unexpected occurrence and the established place of adrenaline in treatment guidelines internationally for more than 10 years, this lack of evidence for a treatment that was introduced well before the evidence-based medicine era is perhaps unsurprising (Sheikh A, 2009).

The Cochrane review concluded that as there are no controlled trials, there is no way to estimate the risk in relation to benefit. However, on the basis of current evidence, the authors concluded that the benefit of using appropriate doses of i.m. adrenaline is likely to far exceed the risk. Anesthetists, who see anaphylaxis relatively commonly, usually have sophisticated monitoring in place before, during and after the event and report a rapid and predictable response to adrenaline that is near universal.

There is a strong clinical impression that prompt injection of adrenaline is life saving in anaphylaxis. However, conducting research in this area is challenging for several reasons, including:

- The established position of adrenaline treatment thereby making it difficult to argue for placebo-controlled trials.
- The ethical issues involved in obtaining informed consent (or deferring consent) in emergency situations.
- Difficulty in conducting double-blind, placebo-controlled studies because of the transient pharmacological effects (pallor, tachycardia, tremor) of adrenaline in standard doses that reverse airway obstruction and circulatory collapse.
- Logistic issues: anaphylactic episodes usually occur without warning, often in a nonmedical setting; differ in severity from one individual to another and from one episode to another in the same individual.
- Difficulty in obtaining baseline measurements.
- The lack of any information on the pharmacokinetics and pharmacodynamics of adrenaline when given to humans during anaphylaxis and a lack of any prospectively

collected information on clinical outcomes, both of which are required to construct valid hypotheses and inform sample size calculations for a clinical trial.

Therefore, recommendations for prompt adrenaline injection are based on a century of clinical use and on fatality studies, (Pumphrey R, 2000), epidemiologic studies and prospective studies. The latter include both dramatic observational nonrandomized uncontrolled studies in patients actually experiencing anaphylaxis at the time of the investigation (Smith P, 1980; Brown S, 2004) and randomized controlled studies in patients not experiencing anaphylaxis at the time of the investigation (Simons F, 1998; Simons F, 2001; Simons F, 2004). In vitro studies relevant to anaphylaxis and studies in animal models of anaphylaxis have also been performed (Sheikh A, 2009).

Justification for dose in acute anaphylaxis

As previously discussed, the intramuscular (IM) route is the route of choice for most healthcare providers. There is a much greater risk of causing harmful side effects by inappropriate dosage or misdiagnosis of anaphylaxis when using IV adrenaline. Given this, the intravenous route should be reserved for those with unresponsive anaphylaxis (Johnston S, 2003).

The adrenaline entry in Martindale states under "Anaphylaxis and anaphylactic shock":

> "A more dilute solution of 1 in 10,000 is used intravenously; the dose is 500 µg (5 ml) given slowly at a rate of 100 µg/min (1 ml/min), stopping when a response has been obtained. Alternatively the UK Resuscitation Council recommends that an intravenous bolus dose of 50 µg should be given, titrated according to response."

The Emergency Treatment of Anaphylactic Reactions: Guidelines for Healthcare Providers (RC (UK), 2008) recommend the following:

> "**Adrenaline IV bolus dose – adult:** titrate IV adrenaline using 50 microgram boluses according to response. If repeated adrenaline doses are needed, start an IV adrenaline infusion. The pre-filled 10 ml syringe of 1:10,000 adrenaline contains 100 micrograms/ml. A dose of 50 micrograms is 0.5 ml, which is the smallest dose that can be given accurately.
>
> **Adrenaline infusion:** An infusion of adrenaline with the rate titrated according to response in the presence of continued haemodynamic monitoring is an effective way of giving adrenaline during anaphylaxis. Use local guidelines for the preparation and infusion of adrenaline."

Children

<u>Cardiopulmonary Resuscitation</u>

Adrenaline (Epinephrine) Injection 1 in 10,000 is not recommended for use in children under 12 years of age.

<u>Acute Anaphylaxis</u>

IM adrenaline is the preferred route for children having an anaphylactic reaction. The IV route is recommended only in specialist paediatric settings by those familiar with its use (e.g., paediatric anaesthetists, paediatric emergency physicians, paediatric intensivists) and if the patient is monitored and IV access is already available. There is no evidence on which to base a dose recommendation – the dose is titrated according to response (RC (UK), 2008). The

recommendation for adrenaline dosing in children with anaphylaxis, based primarily on anecdotal evidence, is to inject 0.01 mg/kg, up to 0.30 mg (Sicherer S, 2007). Martindale also states that most regimens are based on a dose of 10 µg/kg.

IV.4 Clinical safety

Adrenaline has a relatively narrow therapeutic window (relative benefit vs. risk). Common pharmacological effects that occur at recommended doses via any route of administration include anxiety, dyspnoea, hyperglycaemia, restlessness, palpitations, tachycardia, tremors, weakness, nausea, vomiting, sweating, dizziness, headache, and coldness of the extremities. Adrenaline causes ECG changes including a decrease in T-wave amplitude in all leads in normal persons.
In patients with Parkinsonian Syndrome, adrenaline increases rigidity and tremor (Mosley A, 2010).

Adrenaline Injection 1 in 10,000 BP contains sodium metabisulphite that can cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals (Roth J, 2004).

Rarely, and usually associated with overdosage or overly rapid rate of intravenous infusion, adrenaline administration might contribute to or cause myocardial ischemia or infarction, pulmonary oedema, ventricular arrhythmias and accelerated hypertension in adults and children alike. Particularly vulnerable populations are those individuals at the extremes of age and those with hypertension, peripheral vascular disease, ischemic heart disease, or untreated hyperthyroidism (increased number of β-adrenergic receptors in the vasculature of these individuals render the myocardium more sensitive to β-adrenergic effects of adrenaline) (Kemp S, 2008; Martindale).

Repeated injections of adrenaline can cause necrosis as a result of vascular constriction at the injection site. Tissue necrosis may also occur in the extremities, kidneys and liver (Martindale).

Adrenaline may delay the second stage of labour by inhibiting spontaneous or oxytocin induced contractions of the pregnant human uterus (Martindale). The SPC for Adrenaline (Epinephrine) Injection 1 in 10,000 will therefore contraindicate the use of adrenaline injection during the second stage of labour (see proposed SPC sections 4.3 and 4.6).

Adrenaline is contraindicated in patients with shock (other than anaphylactic shock), organic heart disease, cardiac dilatation, as well as most patients with arrhythmias, organic brain disease or cerebral arteriosclerosis.

Extreme care is needed in conditions which predispose a patient to adverse effects on the heart, such as hyperthyroidism.

Care should be exercised in patients who suffer from hypertension. The vasopressor effects of adrenaline are exaggerated in hypertensive patients and great care must be taken to avoid severe hypertension in these patients.
Care should be exercised in patients who suffer from diabetes mellitus. In diabetic patients, hyperglycemia, caused by β2-receptor-mediated suppression of insulin release, can occur.

Adrenaline is distributed into breast milk and therefore the proposed SPC will recommend that breast-feeding is avoided in mothers receiving adrenaline injection (see section 4.6 of the proposed SPC).

Adrenaline has direct alpha- and beta-agonist actions and its interactions are complex and may be hazardous. The following are known drug-drug interactions with adrenaline which are listed in current SPCs for marketed formulations of Adrenaline (Epinephrine) Injection 1 in 1,000 in Sweden e.g. Adrenalin Mylan 1 mg/ml. No new drug interactions are expected with the proposed 1 in 10,000 formulation and therefore it is appropriate that the same interactions are included in the SPC for Adrenaline (Epinephrine) Injection 1 in 10,000.

IV.5 Discussion on the clinical aspects

In the primary round, a question regarding the readability of the proposed was raised as a potential serious risk to public health. This was considered of outmost importance considering that Adrenaline is used in an emergency setting. The SmPC has now been revised. Parts of the SmPC text was also harmonized with that of current marketed formulations of adrenaline in Sweden (Adrenalin 1 mg/ml). Each ampoule now clearly states the strength of the solution as 0,1 mg /ml to avoid mix-up with other available strength (1mg/ml).

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Beneficial effects
Anaphylaxis is a severe, life-threatening, generalised/systemic hypersensitivity reaction that is rapid in onset and may cause death. Adrenaline is commonly acknowledged as the first line and single most important agent in the treatment of anaphylaxis.
The use of adrenaline is recommended in all international resuscitation guidelines since over 10 years, based largely on animal data and increased short term survival in humans.

Uncertainty in the knowledge about the beneficial effects
There are no data available obtained from placebo-controlled or active comparator-controlled comparative clinical trial due to ethically and medically reasonable constraints.

Unfavourable effects
Usual side effects are tachycardia and hypertension, hyperhidrosis, nausea, vomiting, headache, dizziness, asthenia, tremor and anxiety. Cardiac arrhythmia may follow administration of adrenaline.
Accidental injection into digits in hands or feet may result in peripheral ischaemia requiring treatment. In rare cases stress cardiomyopathy has been seen.

Balance - Importance of favourable and unfavourable effects
There is a wide medical experience that adrenaline has a beneficial effect on possibly life-threatening anaphylaxis reactions and that is documented in well established guidelines. The use of adrenalin in resuscitation is also documented in all well established guidelines. In cases life-threatening emergencies, it is not possible to wave epinephrine administration in any patients.

Benefit-risk balance
The quality of the product, Adrenalin Jacobsen Pharma, is found adequate. There are no objections to approval of Adrenalin Jacobsen Pharma, from a non-clinical and clinical point of view. The product information is acceptable. The application is thus considered approvable.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Adrenalin Jacobsen Pharma, 0,1 mg/ml, solution for injection is recommended for approval.

VI. APPROVAL

Adrenalin Jacobsen Pharma, 0,1 mg/ml, solution for injection was approved in the national procedure on 2014-02-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1658/01/MR	Initial Mutual Recognition Procedure	Yes	17th of January 2017	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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