LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Jext
(adrenaline tartrate)

SE/H/908/01-02/DC

This module reflects the scientific discussion for the approval of Jext. The procedure was finalised at 2010-10-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

ALK-Abelló A/S has applied for a marketing authorisation for Jext, solution for injection in pre-filled pen, 150 microgram, and 300 microgram. The active substance is Adrenaline tartrate. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Jext is presented in the form of a solution for injection containing adrenaline tartrate which corresponds to 150 micrograms or 300 micrograms of the adrenaline base. The excipients are sodium metabisulphite, sodium chloride, hydrochloric acid, and water. The solution for injection is filled in a pre-filled pen.

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, slightly soluble in ethanol and practically insoluble in chloroform and ether. 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

Jext, 150 microgram and 300 microgram, solution for injection is formulated using excipients described in the current Ph. Eur. All raw materials used in the product are of vegetable origin.

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 protected from freezing.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No Potential Serious Risks to Public Health and Other Concerns were raised by CMS or RMS on the non-clinical aspects of Jext.

The applicant has submitted a brief Non clinical overview authored by Dr Peter R. Ryle. This overview lists 31 references, dated 1969 to 2009, and is of acceptable quality.

Jext is a 'second generation' adrenaline auto-injector for the emergency treatment of anaphylactic episodes, which incorporates some novel features compared to the currently available auto-injectors (such as EpiPen). The active principle in Jext is adrenaline tartrate, as opposed to adrenaline in the EpiPen. Adrenaline tartrate brings benefits in terms of stability, shelf-life and wider storage conditions as compared to the adrenaline base in the EpiPen product.

The auto-injector delivers one single dose of either 0.15 ml or 0.3 ml, equivalent to 150 or 300 micrograms of adrenaline, for emergency intramuscular use. The intended use is for the emergency treatment of severe acute allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis.
The 300 microgram dosage is intended for use in adults and children over 30 kg bodyweight. The highest dosage per unit bodyweight that may result from use of the 300 microgram dosage form is therefore 10 µg/kg. The 150 microgram dosage form is intended for use in younger children (15 to 30 kg bodyweight), resulting in a similar dose per unit bodyweight (10 µg/kg) as the 300 microgram dosage form. Adrenaline injections may be repeated at 5 to 15 minute intervals in the absence of clinical improvement after the first injection, therefore the total dose administered during treatment of a single anaphylactic episode could be rather higher than 10 µg/kg bodyweight. The dosage of adrenaline used for treatment of anaphylaxis by the intra-muscular route is normally higher than the dose that that is used for treatment of anaphylaxis by the intravenous route.

Adrenaline has a long history of medicinal use, with recognised efficacy and an acceptable level of safety in the intended indication (acute treatment of anaphylaxis). The active ingredient (and excipients) in Jext have been used extensively for many years in other marketed adrenaline formulations. The difference compared to currently approved adrenaline auto-injector products, is the modified delivery device and the use of the tartrate salt of adrenaline, as opposed to adrenaline base. Adrenaline tartrate is already used in injectable forms of adrenaline. The tartrate salt is also used in combination preparations with atropine and papaverine. On this basis, the marketing application for the Jext auto-injector follows the route of 'well-established use', and therefore, based on Article 10a of the EU Directive 2001/83/EC, pre-clinical studies can be replaced by reference to published scientific literature. In view of the preceding discussion, the applicant has provided a Non-clinical Overview based on the known pharmacological and toxicological properties of adrenaline, as derived from the scientific literature.

III.2 Pharmacology

The formulation is a clear and colourless solution (pH = 3.0 to 4.0 during shelf-life) intended for intramuscular injection using the auto-injector device.

The solution contained within the auto-injector has the following composition:

Active ingredient: Adrenaline tartrate EP 2mg/ml equivalent to 1mg/ml adrenaline base
*Excipients:*Sodium metabisulphite (E223), Sodium chloride, Hydrochloric acid 2M (for pH adjustment) and Water for injection

Primary Pharmacodynamics
Adrenaline exerts multiple pharmacological actions through its action as a potent stimulant of both α- and β-adrenergic receptors, and its effects on target organs are complex (Table 1). In the setting of acute hypersensitivity reactions, stimulation of β_2 adrenergic receptors by adrenaline causes bronchodilation and suppression of release of mediators such as histamine and leukotrienes from mast cells. This, in turn, relieves the itching, hives, and swelling of the lips and tongue. The cardiovascular effects of adrenaline (increased heart rate and systolic blood pressure, peripheral vasoconstriction) are responsible for counteracting the hypotension that occurs during an anaphylactic episode. Stimulation of α_1 adrenergic receptors also reduces mucosal oedema.

Table 1. Pharmacology of Adrenaline.

Receptor	**Pharmacological Effect**
α_1	↑ vasoconstriction, ↑ peripheral vascular resistance, ↓ mucosal oedema
α_2	↓ Insulin release, ↓ noradrenaline release
β_1	↑ Inotropy, ↑ chronotropy
β_2	↑ Bronchodilation, ↑ vasodilation, ↑ glycogenolysis, ↓ mediator release (histamine, leukotrienes) from mast cells/basophils

Secondary Pharmacodynamics
The secondary pharmacodynamic effects can all be predicted from the known pharmacological effects of adrenaline. This is reflected in the typical side effects seen with use of adrenaline in the treatment of anaphylaxis. These typically relate to cardiac over-stimulation (tachycardia, hypertension, arrhythmias, ventricular fibrillation), or symptoms related to temporary induction of an 'anxiety state' due to adrenaline administration (nausea, vomiting, dizziness, headache, asthenia, tremors, fearfulness, agitation). Severe hypertension after adrenaline overdose can cause cerebral haemorrhage and pulmonary oedema. Severe secondary pharmacological effects, particularly in life-threatening cases of anaphylaxis can be successfully and easily treated with α- and β- adrenergic blocking agents, or through use of a combined α/β blocking agent such as labetalol. Adrenaline is also thought to have a direct toxic effect on the skin, in addition to the effects related to induction of ischaemia, this toxicity appearing to be mediated through β-agonist activity.

Safety Pharmacology
The potential effects of adrenaline on the key organ systems (cardiovascular, respiratory and central nervous system) can all be predicted from knowledge of the pharmacological activity of the substance. In accordance with Section 2.9 of the ICH guideline for Topic S7A (Safety Pharmacology Studies for Human Pharmaceuticals), safety pharmacology studies are not necessary for salts of substances that show similar pharmacokinetics and/or pharmacodynamics to previous forms of the substance.

Pharmacodynamic drug interactions
There is potential for interaction of adrenaline with co-administered agents. This interaction are mostly due to the pharmacology of adrenaline and includes;

- Drugs that sensitise the heart to arrhythmias increase the arrhythmia risk after adrenaline administration.

- More pronounced hypertension may occur when adrenaline is given to patients receiving 'β-blocker' drugs.
- Tricyclic antidepressants may increase the risk of severe hypertension and cardiac arrhythmias after adrenaline administration.
- Anaesthetic agents (halothane, cyclopropane, trichloroethylene) may sensitize patients to risk of adrenaline-induced ventricular arrhythmias and pulmonary oedema, particularly if hypoxia is present.
- The effects of adrenaline on insulin release/sensitivity and peripheral glucose utilisation may lead to impaired blood glucose control in diabetics treated with hypoglycaemic agents.

III.3 Pharmacokinetics

Absorption
Adrenaline is absorbed after oral administration, but it is difficult to achieve pharmacologically active concentrations by the oral route, due to rapid oxidation and conjugation by the gut mucosa and liver. Absorption after subcutaneous administration is slow, due to the local vasoconstrictor effect of the drug. Absorption is more rapid after intra-muscular dosing, although (as stated in the SmPC), absorption after IM dosing may still be delayed due to local vasoconstriction, so that massage of the injection site after administration is advised to enhance uptake.

Distribution
Adrenaline is rapidly distributed to the heart, spleen, glandular tissues, and adrenergic tissues. It readily crosses the placenta and is about 50 % bound to plasma proteins.

Metabolism and Excretion
Adrenaline is rapidly metabolised by oxidative deamination and O-demethylation, catalysed by the enzymes monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT), followed by reduction or by glucuronic acid or sulphate conjugation. The liver is the major site of metabolism, containing high activities of MAO and COMT enzymes. About 70 to 95 % of an intravenous dose is excreted in the urine; of the excreted material, about 80 % is excreted as *O*-methyl metabolites, about 2 % as catechol metabolites, and only 1 % as unchanged drug. The major metabolite excreted in the urine is 3-methoxy-4-hydroxymadelic acid. Other metabolites include 3-methoxy-4-hydroxyphenylacetic acid, conjugated metanephrine, and 3-methoxy-4-hydroxyphenyl ethylene glycol, together with minor amounts of 3,4-dihydroxymandelic acid in free or conjugated form and *N*-methylepinephrine.

III.4 Toxicology

Single-dose toxicity
The applicant has compiled literature data on the acute toxicity of adrenaline (Table 2).

Table 2. Literature acute toxicity data for adrenaline and adrenaline tartrate.

Species	Route	LD50 or lowest lethal dose for adrenaline	LD50 or lowest lethal dose for adrenaline tartrate
Rat	oral	30 mg/kg	NA
Rat	ip	10 mg/kg	NA
Rat	sc	5 mg/kg	8.3 mg/kg
Rat	iv	150 µg/kg	82 µg/kg
Mouse	oral	50 mg/kg	4 mg/kg
Mouse	ip	4 mg/kg	7.8 mg/kg

Mouse	sc	1.47 mg/kg	11.1 mg/kg
Mouse	iv	217 µg/kg	1.78 mg/kg
Dog	sc	5 mg/kg	NA
Dog	iv	100 µg/kg	NA
Cat	sc	20 mg/kg	NA
Cat	iv	500 µg/kg	NA
Rabbit	oral	30 mg/kg	NA
Rabbit	sc	4 mg/kg	NA
Rabbit	iv	50 µg/kg	NA
Rat	im	2 m/kg	NA

Repeat-dose toxicity

The applicant refers to two repeat-dose studies for adrenaline.

1. Daily subcutaneous injection of adrenaline (1 mg/kg/day) to rats for 42 days resulted in the death of 21 % of animals over the treatment period, and a marked reduction in bodyweight gain. Reduced activity, but increased aggression, was observed in adrenaline-treated rats. Organ weight analysis revealed increased heart, kidney, liver and adrenal weights. Serum cholesterol and β-lipoprotein levels were increased, and free fatty acid levels decreased. Histopathological examinations revealed increased thickness and loss of corrugation of membranes of aortic media, as well as thickening of aortic intima (Trzeciak, H.I., et al 1973).
2. Daily subcutaneous injection of adrenaline (0.5, 1, 2 or 4 mg/kg/day) to mice for seven days showed interstitial inflammation, fibrosis and disintegration in the myocardium at dosages of 1 mg/kg/day or greater, with changes at 0.5 mg/kg/day being confined to slight inflammatory cell infiltration and oedema in the myocardium. Co-administration of beta-blocker drugs (propanolol, atenolol) or α-blockers (phentolamine) reduced the severity of the cardiac lesions induced by adrenaline, demonstrating the pharmacological basis for the observed toxicity (Kubota, T., et al 1990).

Genotoxicity

In vitro genotoxicity assays conducted on adrenaline have yielded either negative (*in vitro* cytogenetics) or equivocal (bacterial mutation and sister chromatid exchange assays) results. The RTECS database report for adrenaline refers to negative results in a sperm morphology study in mice, and inconclusive results in a mammalian micronucleus test, the studies being performed as part of the US EPA Genetox programme in 1988.

Carcinogenicity

In accordance with the ICH Guideline for Topic S1A (Need for carcinogenicity studies on pharmaceuticals), carcinogenicity studies are not required for products that are for short term use, or which are used infrequently on an intermittent basis.

Reproductive and developmental toxicity

Several published animal studies indicate that adrenaline could exert an adverse effect on reproductive function. Studies in pregnant sheep indicated that adrenaline (about 0.2 µg/kg, intravenously) caused decreased uterine blood flow, that could compromise the foetus. Placental weights were reduced by continuous infusion of adrenaline (0.72 µg/kg/day) between Days 13 and 19 of gestation in rats. Uterine and placental blood flow were reduced, however foetal weights were unaffected, suggesting that the adrenaline-induced vasoconstriction may not necessarily reduce nutrient supply to the foetus. Various studies have indicated that adrenaline may impair implantation and embryonic and foetal survival. Daily subcutaneous

injections of high adrenaline doses (about 5 mg/kg) to pregnant mice on either Days 1-6 of gestation (pre-implantation) or Days 7-10 of gestation (post-implantation) caused significant reductions in live pregnancies. The effects in the pre- and post-implantation periods could be reduced by co-administration of progesterone, and by injection of prolactin in the pre-implantation period. Subcutaneous injection of adrenaline (600 µg/kg twice daily) to rabbits on either Days 3 to 6, 6 to 7 or 7 to 9 of gestation caused reduced implantations and increased foetal deaths and foetal abnormalities, when given in the post implantation period (Days 6-7 or 7-9). Administration of adrenaline (500 µg/kg/day SC on Days 7 to 10 of gestation) to pregnant hamsters caused increased resorptions, reduced litter size and reduced ossification of the foetal skeleton. Some earlier studies have suggested an effect of adrenaline on morphology of spermatozoa in mice, and ovum transport through the oviduct in rabbits, that could also exert an influence on fertility and reproductive performance.

In humans, use of adrenaline in pregnancy has been associated with a slightly increased incidence of congenital malformations. Infusion of adrenaline in pregnant women induces foetal tachycardia, cardiac irregularities and louder heart sounds.

There are no animal data on the effects of adrenaline in lactation. However, it can be assumed that well-indicated use of adrenaline in nursing mothers should not present any significant risk to the offspring, since pharmacologically active plasma concentrations are not achieved by the oral route.

Local tolerance
Local effects can be expected due to the vasoconstrictor action of adrenaline, and the SmPC and package insert advise massage of the injection site following injection, in order to facilitate absorption and distribution of the administered dose.

Impurities and excipients
The levels of impurities and degradation products detected in stability studies of adrenaline tartrate, as formulated in the Jext auto-injector, are all below the thresholds for reporting, identification and qualification as specified in the ICH Q3A and Q3B guidelines, with the exception of adrenaline sulphonic acid. The observed levels of adrenaline sulphonic acid are significantly below the levels observed in other currently marketed products (ie. Epipen).

The excipients employed in the Jext auto-injector (sodium chloride, sodium metabisulphite, and hydrochloric acid for pH adjustment) are all commonly used pharmaceutical excipients, and have been used for many years in other injectable adrenaline formulations. They are all GRAS listed, all comply with their respective monographs in the European Pharmacopoeia and are included in the FDA Inactive Ingredients Guide for IM injections.

III.5 Ecotoxicity/environmental risk assessment

The treatment is foreseen as a single dose (300 µg) and does not form part of a daily treatment routine. However, in accordance with the Summary of Product Characteristics, there is the potential for more than one dose to be administered in extreme circumstances. The Company has assumed a “worse case scenario” of three doses each of 300 µg based on advice given in Section 4.2 of the proposed SmPC, resulting in a potential maximum daily dose of 900 µg. The Company has used default value for Fpen (0.01%) in the calculation this gives a PEC for the surface water of 0.0045µg/L which is below the action level of 0.01 µg/L cited in the guidance. No other environmental concerns for the use of the product are foreseen and the environmental risk assessment is halted at Phase I, no further data nor is action required. The product is not considered to be a risk to the environment.

III.6 Discussion on the non-clinical aspects

The non-clinical benefit risk balance for the product is considered to be positive.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Potential Serious Risks to Public Health and Other Concerns raised by CMS and RMS at day 105 on the indication for the product were satisfactorily responded to by the applicant and were considered to be resolved at day 120.

The applicant has submitted a brief Clinical Overview authored by Dr Kim Simonsen, Senior Director at ALK Abello, Denmark. This Overview lists 53 references, dated 1973 to 2009, and is of acceptable quality.

Adrenaline is a naturally occurring catecholamine neurotransmitter and hormone, which stimulates the sympathetic nervous system. It has agonist properties in both alpha- and beta-adenoreceptors of the sympathetic nervous system. Adrenaline acts to reduce oedema and vasodilation and suppresses the release of histamines and leukotrienes, while mediating bronchodilation and increasing heart rate and cardiac contraction.

When administered in a state of anaphylaxis, adrenaline prevents worsening of allergic airway constriction, increases blood pressure, and may thus be life-saving (particularly in anaphylactic shock). Although incidence rates of anaphylaxis cannot be accurately determined because of the difficulties of diagnosis, there is consensus from many authorities that incidence seems to be rising, particularly reactions to food. The use of auto-injectors is strongly recommended for patients with idiopathic anaphylaxes, or with triggers that are difficult to avoid. The draft guidelines from the European Academy of Allergology and Clinical Immunology (EAACI) on management of paediatric anaphylaxis list four absolute indications for the prescription of adrenaline auto-injectors: previous cardiovascular or respiratory reaction to food, insect sting, or latex; exercise-induced anaphylaxis; idiopathic anaphylaxis; and food allergy with coexistent asthma. Adrenaline auto-injectors have also been recommended for patients with a history of reaction to small amounts of an allergen or with limited access to nearby care. There are also specific types of food triggers (peanuts, tree nuts, fish and shellfish) that allergologists identify as particularly associated with the risk of severe anaphylaxis reactions.

The risk of recurrence of a severe instance of anaphylaxis for an individual who has experienced anaphylaxis has been estimated to be as high as 1 in 12. The severity of previous reactions is not useful in predicting the severity of future symptoms should anaphylaxis recur. Conversely, many experts conclude that adrenaline auto-injectors are under-prescribed, and a second auto-injection is not always provided even though an additional dose may be warranted within 10 minutes in as many as 36% of instances. The increased availability and accessibility to an adrenaline auto-injector for individuals with triggers that are difficult to avoid, or history of idiopathic anaphylaxis, might be instrumental in successfully averting a lifethreatening attack.

Pharmacokinetics

Adrenaline is metabolised rapidly after administration, mostly by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) in the liver and other body tissues. Adrenaline is mostly excreted as inactive metabolites in the urine with very little unchanged drug present (approximately 1%). The elimination half-life of adrenaline is known to vary based on the route of administration. In a study of 17 children aged 4 to 12 years, intramuscular adrenaline was reported to have an elimination half-life of 43 minutes (± 15). The preferred route of administration for adrenaline in an emergency situation has been established as intramuscular, although intravenous administration may be indicated in severe cases. In a study comparing the pharmacokinetics of adrenaline when administered subcutaneously and intramuscularly, the maximum plasma concentration was achieved in a mean of 8 minutes (± 2) for patients via intra-muscular administration, compared with a mean of 34 minutes (± 14) for subcutaneous administration. The maximum plasma concentration has also been reported as higher in patients who received adrenaline by the intra-muscular route into the thigh, as compared with subcutaneous injection or intra-muscular administration into the arm. The rapidity of achieving peak levels is crucial given the risk of poor outcomes associated with delay of adrenaline administration for patients experiencing anaphylaxis.

Jext is an immediate-release product for intramuscular administration containing a well known active substance in the same concentrations as other products on the market. The only difference is that Jext contains adrenaline tartrate while other adrenaline auto-injectors marketed in the EU are formulated with the adrenaline base. The applicant has verified that there are other adrenaline products containing adrenaline tartrate for intramuscular use approved within the EU. The use of the adrenaline tartrate is not considered to have any significant impact on safety and efficacy compared to adrenaline base. The excipients are the same as in other product on the market.

Pharmacodynamics
No new data are requested or provided for this application.

The optimal dose of adrenaline for anaphylaxis in children and adults has not been definitely established. The recommended dose for adults given in various guidelines ranges from 0.30 to 1.0 mg. This range of recommended doses is due to the variability of individual response and the lack of evidence from controlled trials. However, if an adequate response is not seen within 5-20 minutes, an additional dose can be given, either by emergency personnel or by the use of a second auto-injector if available.

Generally the preferred dose of adrenaline for children is 0.01/mg/kg, up to a maximum of 0.30 mg. This makes a 150 microgram auto-injector suitable for a 15 kg – 30 kg child, and a 300 microgram auto-injector suitable for children and adults weighing more than 30 kg. A fixed dose will however rarely be ideal and a risk/benefit assessment should be performed.

In a paediatric study children where administered with both the 150 and 300 microgram fixed dose adrenaline auto-injectors; the subjects receiving the larger dose showed a higher increase in systolic blood pressure and also more adverse effects. In assessing the risk/benefit of prescribing a child the higher 300 microgram dose, the EACCI guidelines for paediatric anaphylaxis conclude: “mild overdosing of a child with a self-injectable adrenaline device does not seem to represent a major risk in otherwise healthy children.” It is not recommended that children weighing less than 10 kg be administered an adrenaline auto-injector.

Clinical efficacy

As there have been no relevant randomised trials conducted, and much of the relevant data is anecdotal and retrospective, no tabulations were prepared by the applicant of the data quoted in the literature for this application. The well established efficacy of adrenaline in the treatment of acute anaphylaxis is derived from extrapolation of its pharmacological effects, from a long history of conventional use with anecdotal support, and from retrospective reviews of fatal and near-fatal anaphylactic shocks. There is international consensus from the relevant medical organisations that adrenaline is extremely effective for the immediate relief of moderate to life-threatening symptoms from acute anaphylaxis. The acceptance of adrenaline as an efficacious treatment for acute anaphylaxis is indicated by the large number of prescriptions issued for the indication (over 100,000 in the UK in 2001). Anaesthesiologists with considerable experience report a predictable response to adrenaline in patients experiencing anaphylaxis. In a pilot program assessing out-of hospital use of adrenaline by emergency personnel, 77% of patients experiencing an allergic attack showed an improvement after dosing (with 20% unchanged and 3% showing further deterioration).

In retrospective analyses of severe anaphylaxis reactions, poorer outcomes correlate with a lack of adrenaline administration within 30-60 minutes of the initial onset of symptoms. In a review of 63 food anaphylaxis fatalities in the United States, only 7 patients had access to adrenaline auto-injectors at the time of the reaction. In a follow-up to this report with more recent fatalities, it was noted that in only 4 of 31 fatal cases did it appear that adrenaline was administered in a timely manner. A similar retrospective analysis of anaphylaxis deaths in the United Kingdom between 1992 and 2000 revealed that, while adrenaline was administered in 62% of cases, it was only given prior to respiratory or cardiac arrest 14% of the time, highlighting the importance of early administration. In a review article of 6 fatalities and 7 near fatalities (requiring intubation) following episodes of food-related anaphylaxis in children, it was noted that 5 of the 7 survivors were administered adrenaline within 30 minutes, while only 1 of the patients who died received adrenaline within an hour. In a study of 27 severe anaphylactic reactions which occurred outside of the hospital setting, adrenaline was administered to 78% of the patients; 2 of these patients died, and both deaths occurred after delays in treatment of longer than 45 minutes following the onset of symptoms. In a review of 7 patients that suffered fatal food anaphylaxis, adrenaline was not immediately administered in any of the cases, and over-reliance on oral antihistamines to treat symptoms was cited as a factor contributing to the severity of the reactions.

As adrenaline degrades rapidly, auto-injectors should be replaced after expiry.

Clinical safety

Severe and/or fatal instances of anaphylaxis are often associated with late administration of adrenaline and the availability of a therapeutic dose of adrenaline before the arrival of emergency personnel could be potentially life-saving.

The European Resuscitation Guidelines conclude that intra-muscular administration of adrenaline is “very safe”. There are commonly reported transient side effects including pallor, agitation, headache, tremor, dizziness anxiety, and palpitations. More serious cardiac adverse events have also been associated with adrenaline. Such reactions are reported with overdose or intravenous administration and not in relation to a single fixed intra-muscular dose. The only reported myocardial infarction after intra-muscular injection of adrenaline was in a patient with multiple risk factors for coronary disease.

There are several drugs that can adversely affect adrenaline if taken concomitantly. ACE inhibitors and beta-blockers may reduce the effect of adrenaline and a careful review of these medications should be undertaken in conjunction with the prescription of an adrenaline auto-

injector. There may be an increased risk of adverse effects such as hypertension or arrhythmia in patients taking tricyclic antidepressants or monoamine oxidase (MAO) inhibitors, catechol-O-methyl transferase inhibitors (COMT inhibitors), in cocaine users, or in patients with ischemic heart disease or uncontrolled hypotension. However, the UK Resuscitation Council guidelines specifically recommend against dosing caveats for patients at increased risk of adverse events or reduced efficacy when considering the initial treatment of acute anaphylaxis. The timely administration of adrenaline is critical and, during follow-up in a hospital setting, physicians can give additional doses to provoke a greater response or provide further intervention for adverse effects, if needed.
The risk of unintentional injection does exist, particularly in users with inadequate training. However, in a retrospective study involving cases of accidental injection by adrenaline auto-injectors (91% of which involved a thumb or another finger), no permanent sequelae were reported.

Pharmacovigilance system
The Market Authorisation Holder has provided satisfactory response to the questions raised in connection with the review of the updated DDPS. The responses shall be implemented in the next version of the DDPS the company commits to do.

Thus, the MPA considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
Risk minimisation activities include plans in order to minimise the number of cases with accidental injections, and where the injector does not work in a critical situation. The activities include a training device, which is available in all countries where Jext is marketed. This is also mentioned in the Jext SmPC and PIL. Educational material in the national language should also be available in all countries where Jext is marketed. The latest version of the RMP has been accepted.

Safety concern	Routine risk minimisation activities sufficient?	If Yes, describe routine activity and justification
Identified risks		
Accidental injection	Routine risk minimisation activities have been implemented in the SmPC and PIL for Jext. Further risk minimisation activities have been described in Part II section 4 of this RMP. The risk minimisation activities includes a Jext training device (The Jext simulator). The Jext Simulator is available in all countries where Jext is marketed. Educational material (printed material and website material) in the national language is also available in all countries where Jext is marketed. The purpose of these risk minimisation activities is to limit the number of accidental injections in patients and caregivers.	Peripheral ischemia following accidental needle stick is listed in section 4.4 and 4.8 of the SmPC. In order to avoid accidental needle stick, clear instructions on how to use Jext is provided in the PIL with pictograms. The labelling on the pen also provides a clear instruction on how to use the pen. In order for the patient to train in how to use Jext Simulator pens are available to to physicians, patients and caregivers. A needle protector in Jext prohibits accidental needle stick when the pen is discarded after use, which is expected to reduce this risk. Internal surveillance every 3rd month is considered sufficient. This allows the applicant to analyse data to identify risk-factors not identified during the clinical programme and address these in a focused manner if needed.
Auto-injector not working in a critical situation	Routine risk minimisation activities have been implemented in the SmPC and PIL for Jext. Further risk minimisation activities have been described in Part II section 4 of this RMP. The risk minimisation activities includes a Jext training device (The Jext simulator). The Jext Simulator is available in all countries where Jext is marketed. Educational material (printed material and website material) in the national language is also available in all countries where Jext is marketed. The purpose of these risk minimisation activities is to limit the number of cases where the auto-injector is not working in a critical situation.	In order to avoid that the Auto-injector is not working in a critical situation clear instructions on how the use Jext is provided in the PIL with pictograms. The labelling on the pen also provides a clear instruction on how to use the pen. In order for the patient to get familiar with how to use Jext, Simulator pens are available to physician, patients and caregivers. Internal surveillance every 3rd month is considered sufficient. This allows the applicant to analyse data to identify risk-factors not identified during the clinical programme and address these in a focused manner if needed.

Lack of drug effect	Yes	It is stated in the SmPC and in the PIL that a second Jext injection may be administered after 5-15 minutes if the symptoms are still present after the first injection. It is furthermore stated in section 4.4 of the SmPC that the patient should seek emergency medical assistance immediately after administering the first dose in order to have close monitoring of the anaphylactic episode and further treatment as required. Internal surveillance is considered sufficient. This allows the applicant to analyse data to identify risk-factors not identified during the clinical programme and address these in a focused manner if needed.

IV.2 Discussion on the clinical aspects

All outstanding issues have been resolved satisfactorily and the benefit risk balance for the product is considered to be positive.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the product EpiPen. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Jext, solution for injection, 150 microgram and 300 microgram is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Jext, solution for injection, 150 microgram and 300 microgram, was successfully finalised on 2010-10-12.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/908/01-02/II/25	This variation application concerns the submission of a PK/PD study report for Jext in accordance with the Commission implementing decision (C(2015)5886) of 14 August 2015 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations of "Adrenaline auto injectors" medicinal products for human use (EMA/H/A-31/1398)	SmPC, PL	2018-10-17	Approval	In accordance with the Commission decision following the Art 31 referral procedure for adrenaline autoinjectors, each MAH conducted 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 results from a PK/PD study (JX-A-03) has been provided. In the study administration of Jext 300 µg autoinjector was compared to IM adrenaline administration in three cohorts of subjects according to skin to muscle depth (STMD).

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					There was a large variability in shape of the individual plasma concentration-time profile.The adrenaline absorption is comparable following injection of Jext and by IM syringe in the low and medium STMD cohorts. However, in subjects with the largest STMD (>20 mm) there was an indication of a slower absorption following administration of Jext compared to IM syringe that may result in a suboptimal effect. The product information has been updated to reflect the results.

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