LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

EpiPen Twist, EpiPen Jr. Twist
(adrenaline tartrate)

SE/H/2514/01-02/DC

This module reflects the scientific discussion for the approval of EpiPen Twist, EpiPen Jr. Twist. The procedure was finalised at 2026-03-18. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for EpiPen Twist, EpiPen Jr. Twist, 300 mikrogram, 150 mikrogram, Solution for injection in pre-filled pen.

The active substance is adrenaline tartrate, adrenaline. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

Anaphylaxis is an acute, potentially life-threatening hypersensitivity reaction that can be triggered by e.g. various provoking agents ingested via food or medications, latex exposure, and insect toxins. Most cases are mild, but the condition has a potential to become life-threatening. The incidence of anaphylaxis is difficult to estimate but mortality is overall low.

Symptoms arise from many organ systems, but severe cases may notably involve loss of consciousness, airway obstruction and circulatory collapse. Anaphylaxis develops rapidly, usually reaching peak severity within 5 to 30 minutes, and may, rarely, last for days. The severity of an anaphylactic episode can be expected to differ between patients and in the same patient from one episode to another. At the onset, it is not possible to predict whether the patient will recover spontaneously, respond promptly to treatment, progress to a severe condition, or die within minutes.

Adrenaline is since many decades well-established as an effective key component in the emergency treatment of anaphylaxis. Since clinical trials in anaphylaxis are essentially unfeasible the dosing recommendations in international consensus clinical guidelines rests on expert opinion and clinical experience. The lack of a distinct rationale for definitive dosing is in the healthcare setting overcome by titration to effect in the individual patient. Due to the emergent nature of the condition, prehospital self-administration is an important opportunity for early treatment, but this should only be seen as a bridge to emergency healthcare and should not be seen as definitive treatment.

II.2 About the product

As a nonselective adrenergic agonist, adrenaline increases peripheral vascular resistance through vasoconstriction, increases cardiac output, contributes to reverse bronchoconstriction and mucosal oedema, and is also said to stabilize mast cells and basophils. The product is a newly developed autoinjector (T005 ERAI) with adrenaline, intended for use by lay persons as a bridge to emergency healthcare. The product is therefore accompanied by an educational programme. See section I for the claimed indication.

According to the Applicant, in the present WEU application a new autoinjector was developed – denoted through the document as “T005” ERAI (Emergency Response Auto-injector). It is as an update to existing EpiPen Auto-Injectors (EpiPen® and EpiPen Jr®), which are registered as Fastjekt® (MA no.13579.00.00) and Fastjekt Jr.® (MA no.65312.00.00) in Germany; also approved under the following registration: SE/H/0137/01-02/MR for EpiPen and EpiPen Jr, and SE/H/1287/01-02/DC for Nepipe and Nepipe Jr (in other European countries) and also approved under the following registrations in United Kingdom (UK): EpiPen Adrenaline Auto-injector 0.3mg (PL 46302/0171) & EpiPen Jr. Adrenaline Auto injector 0.15mg (PL 46302/0172) [UK National licences].

T005 ERAI has an automated drug delivery and similar characteristics as the current EpiPen, including activation force, delivered volume and drug ejection time. The differences are:

- Salt form of adrenaline - T005 ERAI uses tartrate salt form of adrenaline and the current EpiPen contains adrenaline in the base form.
- Simplified user process

II.3 General comments on the submitted dossier

The application for EpiPen Jr. 150 µg/ EpiPen 300 µg, solution for injection in pre-filled pen, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SI, SK as concerned member states (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP

A statement on the application of appropriate GCP standards in the submitted study has been provided.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

This is a well-established use application which is solely based on bibliographic data. Adrenaline/epinephrine has been studied extensively in various preclinical models and there is a long clinical experience with the substance. No new non-clinical data have been submitted, and none are required.

III.3 Clinical aspects

Pharmacokinetics

As a part of the present WEU application the Applicant has presented a brief overview of available literature data regarding the PK of adrenaline, as well as one clinical study (denoted as EPIN-IJS-1001) with the new drug product including a newly developed autoinjector T005 ERAI.

Overall, the literature references about the clinical pharmacokinetics of adrenaline presented by the Applicant are limited but considered sufficient for the present WEU application and sufficient to inform the SmPC claims in terms of pharmacokinetics.

Discussion and overall conclusion

In 2015, article 31 referral procedure was initiated for adrenaline auto-injectors (EMEA/H/A-31/1398), resulting in each Marketing Authorisation Holder (MAH) of adrenaline auto-injectors performing a PK/PD study to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via their adrenaline auto-injector device. The overall study design is in accordance with the recommendations from the referral procedure.

For a WEU application, the application must be based on published literature and a bridge between the applied product and the literature is required in terms of a PK/PD study. EPIN-IJS-1001 supports bridging to the submitted literature data.

A fast onset of action is important in the treatment of anaphylaxis and thus a fast absorption of adrenaline is crucial. Adrenaline was rapidly absorbed following administration with both Epipen and the IM syringe. One concern with adrenaline autoinjectors has been whether adrenaline is administered intramuscularly or subcutaneously. Especially in subjects with high skin-to-muscle-depth (STMD), there may be a risk of subcutaneous injection which may result in a slower absorption and delayed effect. This risk has been described in the SmPC.

Pharmacodynamics

The catecholamine adrenaline is a potent agonist effects on both alpha and beta-adrenergic receptors. Different sensitivity of different receptors leads to variable pharmacodynamic response in relation to the specific exposure level. The pharmacodynamic effects of key importance for the treatment of anaphylactic reactions are vasoconstriction, increased heart rate, bronchodilatation, and inhibition of release of inflammatory mediators from mast cells. The pharmacodynamic profile of relevance for the treatment of anaphylaxis is well characterised by the literature provided in the application.

Clinical efficacy

Anaphylaxis is a life-threatening medical emergency. The occurrence is unpredictable, as is the severity and progression of the event. The absence of clinical trial data to support the efficacy of adrenaline is consequently self-evident. The conduct of clinical trials is in that context neither ethical nor feasible. Studies in more controlled situations, such as in clinical antigen provocation tests, are feasible and have been performed but these studies are then largely restricted to milder reactions and very early treatment. Unfortunately, the major uncertainty lies in the efficacy in more severe anaphylaxis.

Adrenaline is by broad consensus recognized as the first-line treatment for anaphylaxis. This is based on case series with reviews of medical records and consensus expert opinion expressed since decades in international guidelines, and well reflected by the literature submitted with this application. The posology proposed is in line with guideline recommendations and therefore acceptable.

The bioavailability study submitted by the Applicant provides support for an exposure largely comparable to what is expected in relation to manual IM injection. The study provides a bridge from the autoinjector device to the literature referred to in this application.

It should be recognised that there are no specific exposure levels that can be stated as required for efficacy. A threshold level of 100 pg/ml for a pharmacodynamic effect on blood pressure is sometimes referred to. In an experimental study increments in systolic blood pressure were seen at concentrations of 75-125 pg/ml. It should be acknowledged that this is based on 6 normal subjects (5 men and 1 woman), aged 25-38 years. The results from this experimental study on adult heathy volunteers do not provide meaningful and reliable evidence to inform the posology of adrenaline in the treatment of anaphylaxis.

Considering the results of the bioavailability study it should further be acknowledged that there are no data that have evaluated whether the peak plasma concentration, the time to peak plasma concentration, or the area under the curve is the most important feature for effective adrenaline exposure in anaphylaxis. The assessment of the exposure profiles must therefore rest on contextualisation against previously approved adrenaline products, and acknowledging the variability seen with such products and the lack of a defined target exposure pattern defining efficacious and safe threshold levels.

Variability is expected, e.g. in relation to skin to muscle distance. This was the topic of the referral procedure under Article 31 of Directive 2001/83/EC finalised in 2015. The PK/PD studies conducted

in the aftermath of this procedure demonstrated substantial variability in exposure, which could not be explained by the skin to muscle distance alone. High BMI is, however, associated with an increased risk for SC injection instead of the intended IM injection, and this is adequately reflected in the product information.

For this new device, the extended needle length has also been adequately justified based on the available literature and related considerations. It is, however, noted that the concentration-time profile observed for the group with longest STMD is different in the bioavailability study (see section III.3). This is expected and the potential consequences are difficult to assess. As already stated, there is no specific threshold concentration to benchmark against as required or sufficient, and there is no specific PK parameter established to be of pivotal importance. Furthermore, the bioavailability study is performed in normal subjects and not in the situation of anaphylactic shock. In that situation there is a redistribution of blood flow, and uptake may be different. In anaphylactic shock there is an abnormal redistribution of blood flow to peripheral tissues, and uptake from the subcutis may actually be higher than in normal subjects. In older guidelines also subcutaneous injection was recommended and there are no actual observations of poor effect from those recommendations. It is therefore sufficient to present the data on uptake in the product information and provide warnings that the needle length may not ensure intramuscular injection in patients with a long STMD. Section 4.4 of the SmPC adequately states that "*In patients with thick sub-cutaneous fat layer, there is a risk for adrenaline not reaching the muscle tissue resulting in a suboptimal effect (see section 5.2)*".

From a clinical perspective the ENL is by necessity a compromise, to fit an as large proportion of the target population as possible. The justification provided for the ENL based on literature data, also for paediatric patients, supports that it is a reasonable compromise but the adequacy of the ENL still needs to be considered for the individual patient.

The need for more than one injection is seen in approximately 1/10 cases according to the provided literature. The recommendation for a second dose and to always carry two devices has therefore been sufficiently justified from the literature review.

Overall, efficacy is sufficiently characterised and supported by the literature provided.

The agreed wording of the indication reads:

> *TRADEMARK Auto-Injector (adrenaline) is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to e.g. insect stings or bites, foods, drugs and other allergens, as well as idiopathic or exercise induced anaphylaxis.*

Clinical safety

The safety profile is related to the known pharmacodynamic effects of adrenaline. Adverse events in the emergency treatment of anaphylaxis have been described based on published case series with retrospective medical record reviews. Overall, the safety profile suggests mainly mild symptoms compatible with expected pharmacodynamic effects of adrenergic stimulation. Adverse reactions and potential interactions of relevance described in the product information are an adequate reflection of the literature review provided in the application.

The well-known safety concern with accidental digital injection by auto-injector is adequately described in the provided literature. While the accidental injection itself may not be a serious safety concern, the loss of a dose for the anaphylactic patient may be critical. Safety of the device and adequate training are cornerstones to minimise this risk.

There are no outstanding issues with special populations.

Pharmacovigilance system

Proposed MAH: Viatris AB, Viatris Healthcare Limited, Viatris Austria GmbH, Viatris Healthcare nv/sa, Viatris ApS, Viatris Hellas Ltd., Viatris Oy, Viatris Mecial, Viatris Hrvatska d.o.o., Viatris AS, Viatris Healthcare Lda.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to the product.

Part II Safety specification

Summary of Safety Concerns	
Important Identified Risks	• Device failure • Accidental injection • Lack of efficacy (due to wrong handling or lack of efficacy when no wrong handling or device failure was reported)
Important Potential Risks	• Serious allergic reaction to sodium metabisulfite content of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector • Serious cardiovascular adverse reaction in predisposed patients
Missing Information	None

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Device failure - Important Identified Risk	Routine risk minimization measures Additional risk minimisation measures: • Educational material	Routine pharmacovigilance activities and intensified follow-up. Intensified follow-up of post-marketing data includes: • MAH will continue to ask the reporter in case of device failure or technical problems to send in the device • MAH will clearly identify cases of inability to administer the drug • After identification of these cases a clear distinction between device failure (technical problems) and handling error is required.
Accidental injection - Important Identified Risk	Routine risk minimization measures Additional risk minimisation measures: • Educational material	Routine pharmacovigilance and intensified follow-up Intensified follow-up of post-marketing data includes: MAH will continue to ask the reporter in case of device failure or technical problems to send in the device. • MAH will clearly identify cases of inability to administer the drug • After identification of these cases a clear distinction between device failure (technical problems) and handling error is required
Lack of efficacy (due to wrong handling or lack of efficacy when no wrong handling or device failure was reported) - Important Identified Risk	Routine risk minimization measures Additional risk minimisation measures: • Educational material	Routine pharmacovigilance activities and intensified follow-up Intensified follow-up of post-marketing data includes: • Clear identification of cases of lack of efficacy where it was suspected that the drug was not administered correctly or the drug was administered correctly but the given dose was not effective • Targeted follow-up will be done for cases of lack of efficacy, where it was suspected that the drug was administered correctly but the given dose was not effective, to capture also the body weight.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious allergic reaction to sodium metabisulfite content of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector - Important Potential Risk	Routine risk minimization measures	Routine pharmacovigilance activities
Serious cardio-vascular adverse reaction in predisposed patients - Important Potential Risk	Routine risk minimization measures	Routine pharmacovigilance activities

Educational material:

1. Training device which should allow prescribers and patient/carers to familiarise themselves with the device and the administration procedure of the prescribed adrenaline Auto-Injector before its actual use. The training device mimics the precise step of use of the active device without containing the active substance or a needle and offer the possibility to be reset and used repeatedly.

1. Instructional material
    a. Instructional audio-visual material which explains in detail how the product is to be used and the different steps for administration.
    b. Printed educational material

2. Checklist for prescribers aiming to facilitate the discussion between the prescriber and the patient and to provide sufficient information on the optimal way of use, administration and storage of the product.

The educational material will be available on the local websites or by directly contacting the local offices by mail. Furthermore, it is possible to directly watch the “How to use EpiPen tutorial” by scanning the QR-code which will be implemented on the outer packaging (cartons).

Part VI Summary of the RMP

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.3 signed 26-Jan-2026 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

Anaphylaxis is a life-threatening medical emergency. The occurrence is unpredictable, as is the severity and progression of the event. The absence of clinical trial data to support the efficacy of adrenaline in severe anaphylaxis is consequently unavoidable. The conduct of clinical trials is in that context neither ethical nor feasible. Self-administration of adrenaline is, however, broadly recognized in international consensus guidelines as the first-line treatment for anaphylaxis.

The product's quality has been thoroughly demonstrated through a comprehensive development process, during which both the medicinal product and the device have been well described and investigated. Extensive controls are in place throughout the manufacturing process to ensure the product's quality and reproducibility. Furthermore, sterility is guaranteed through rigorous monitoring during the aseptic manufacturing process. From a quality perspective, the product is recommended for approval.

From a clinical perspective the provided literature provides sufficient support to characterise efficacy and safety. Concerns for potential medication errors related to the introduction of a new device have been considered. The concern is partly related to the product name. An appropriate product name has been agreed with the concerned member states to minimise the risk for medication errors. Other appropriate measures have also been taken to minimise the risk, including the adaptations of the product information and the educational material. A checklist for prescribers is also a relevant additional risk minimisation measure to help mitigate the potential risk for medication errors. The Human Factors Validation Study, and the measures taken by the Applicant based on those results, do not identify any notable current concern for medication errors with the new product.

It follows that a DHPC is not considered warranted. It would have substantial promotional aspects and is not considered justified by available safety data at this stage. The MAH may, however, within the

rules and restrictions for promotional activities, target individual prescribers with information regarding the new product. This should not be labelled as important safety information.

The benefit-risk balance is favourable.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  The educational material should contain the following key elements:

  - Training device which should allow prescribers and patient/carers to familiarise themselves with the device and the administration procedure of the prescribed adrenaline Auto-Injector before its actual use.
    The training device mimics the precise step of use of the active device without containing the active substance or a needle and offer the possibility to be reset and used repeatedly.
  - Instructional audio-visual material which explains in detail how the product is to be used and the different steps for administration.
  - Checklist for prescribers aiming to facilitate the discussion between the prescriber and the patient and to provide sufficient information on the optimal way of use, administration, and storage of the product.

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 language used for the purpose of user testing the PL was English.

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 user test was assessed and accepted at day 120.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-