VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

The incidence of anaphylaxis is 4–5 per 100,000 persons/year (Lee & Vadas 2011), with a lifetime-risk of 0.5–2 % (Simons et al. 2011). Rates appear to increase: incidence in the 1980s was 20 per 100,000/year, while in the 1990s it was 50 per 100,000/year (Simons 2009). The increase appears to be primarily for food-induced anaphylaxis (Koplin et al. 2011). The risk is greatest in young people and females (Simons 2009, Lee et al. 2011).

Currently, anaphylaxis leads to approximately 1500 deaths/year (Neugut 2001) (4.7/million) in the US, 20 deaths/year in the UK (0.33/million), and 15 deaths per year in Australia (0.64/million) (Lee et al. 2011). Mortality rates have decreased between the 1970s and 2000s (Demain et al. 2010). In Australia, deaths from food-induced anaphylaxis occur primarily in women while deaths due to insect bites primarily occur in males. Death from anaphylaxis is most commonly triggered by medications (Lee & Vadas 2011).

VI.2.2 Summary of treatment benefits

Epinephrine injected intramuscularly is the drug of choice for the treatment of systemic anaphylactic reactions irrespective of aetiology because of its ability to counteract the vasodilation (dilatation of blood vessels), bronchoconstriction (constriction of the airways), and most of the other adverse effects of anaphylactic mediators and to inhibit their further release from mast cells and basophils (immune cells; Bochner & Lichtenstein 1991, Fisher 1992, Fisher 1995). There is consensus on the use of epinephrine as first line treatment of anaphylaxis, as it is the only pharmacological intervention with proven lifesaving properties (Rutkowski et al. 2012).

There are no data available obtained from placebo-controlled or active comparator-controlled comparative clinical trials. In emergency patients, neither the medical circumstances nor the patients' condition allow conventional (written) informed consent procedures. These clinical settings are hardly suitable for the experimental settings of randomised, controlled, blinded clinical trials, also with regard to the need for standardisation of the treatment conditions and surveillance thereof.

These issues need to be taken into account when evaluating the extent and nature of the clinical documentation and/or appropriateness thereof. Nevertheless, the body of pharmacology-based rationale and medical experience/evidence consistently indicate epinephrine as the treatment of choice in anaphylaxis.

VI.2.3 Unknowns relating to treatment benefits (1 short paragraph per indication of 50 words maximum)

Epinephrine is commonly acknowledged as the most important first-line treatment of severe allergic emergencies, as it is recognized as the only pharmacological intervention with proven lifesaving properties. Therefore, there are no known absolute contraindications to the use of EpiPen® and lack of information is not considered relevant.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Device failure	This medication error can occur due to technical problems of the device. The failure of an Auto-Injector puts the patient at potentially life-threatening risk. Therefore, the medication error is considered as important identified risk.	If one Auto-Injector does not work in a critical situation the patient will require another EpiPen® or another form of emergency treatment. To optimise anaphylaxis treatment the patient should carry more than one Auto-Injector all the time with him. Provision of an EpiPen® Auto-Injector double-pack is intended to optimise anaphylaxis treatment, as in the absence of clinical improvement or if deterioration occurs after the initial treatment, a second injection may be necessary after 5 to 15 minutes. The labelling of EpiPen® (SmPC and Package Leaflet) supports carrying two Auto-Injectors, stating that if symptoms have not improved or have deteriorated within 5-15 minutes after the first injection, a second dose of EpiPen® may be necessary. To ensure that professionals and patients/carers are able to successfully administer the product based on the instructions in the product information, the MAH offers a range of educational material (training device, instructional audio-visual material, checklist for prescribers).
Accidental injection	Accidental injections into thumb, fingers or the hand may result in ischemic effects. The impact on the individual patient depends on the course and the severity of the reaction due to accidental injection. Accidental injections can occur by patients themselves or by health care professionals when attempting to treat the patient. In case the injection was not administered in a proper form, this misadministration puts the patient suffering from anaphylaxis at significant risk.	An adequate instruction and training is of importance for the correct use of epinephrine Auto-Injectors, particularly among younger patients. Therefore, the Package Leaflet includes comprehensive directions of the use of EpiPen® Auto-Injector. Furthermore, the MAH offers a range of educational material to ensure that healthcare professionals and patients/carers are able to successfully administer the product based on the instructions in the product information (training device, instructional audio-visual material,

Risk	What is known	Preventability
		checklist for prescribers). Additionally, within the SmPC the physician is indicated to ensure that the patient understands the indications for use and the correct method of application.
Lack of efficacy (due to wrong handling or lack of efficacy when no wrong handling or device failure was reported)	Lack of efficacy of epinephrine in case of an anaphylactic emergency puts the patient at potentially life-threatening risk. Therefore, the lack of efficacy is considered as important identified risk.	Patients should be well trained in the use of the EpiPen® Auto-Injector and should have an adequate amount of EpiPen® Auto-Injectors at hand. In particular early intervention with i.m. epinephrine is most essential for the successful treatment of patients having an anaphylactic reaction. Treatment at the emergency ambulance or in the emergency room might be required by patients not responding. In the PIL patients are advised “to seek medical help immediately after using EpiPen®, by going to your doctor or the nearest hospital”. Provision of an EpiPen® Auto-Injector double-pack is intended to optimize anaphylaxis treatment, as in the absence of clinical improvement or if deterioration occurs after the initial treatment, a second injection may be necessary after 5 to 15 minutes. The approved labelling of EpiPen® (SmPC and Package Leaflet) supports carrying two Auto-Injectors, stating that if symptoms have not improved or have deteriorated within 5-15 minutes after the first injection, a second dose of EpiPen® may be necessary. Under section 4.4 “special warnings and precautions for use” of the SmPC it is stated, that patients should be instructed to dial 112, ask for ambulance, state anaphylaxis to seek emergency medical assistance immediately after administering the first dose in order to have close monitoring

Risk	What is known	Preventability
		of the anaphylactic episode and further treatment as required. Furthermore, it is mentioned that for patients with thick subcutaneous fat layer, there is a risk for adrenaline not reaching the muscle tissue resulting in a suboptimal effect. In addition, the MAH offers a range of educational material to ensure that healthcare professionals and patients/carers are able to successfully administer the product based on the instructions in the product information (training device, instructional audio-visual material, checklist for prescribers).

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Serious allergic reaction to sodium metabisulfite content of EpiPen®	Sodium metabisulfite may rarely cause severe hypersensitivity reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma.

Risk	What is known (Including reason why it is considered a potential risk)
Serious cardiovascular adverse reaction in predisposed patients	Important clinical risk factors for serious cardiovascular adverse reactions under EpiPen® (Jr.) therapy include comorbidities such as pre-existing increased blood pressure or cardiac valve disease.

Missing information

None.

VI.2.5 Summary of risk minimisation measures by safety concern

For all safety concerns, routine risk minimisation measures, including special warning in the SmPC, CCDS or PIL, are applied.

These additional risk minimisation measures are for the following risks:

Important identified risk: Device failure

Risk minimisation measures
Objective and rationale: • The aim of the risk minimisation measure is to monitor the number of device failures and to ensure that even in case of device failure, the life-threatening situation may be adequately treated.
Summary description of main additional risk minimisation measures: Educational material includes: - 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.

Risk minimisation measures
- 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.
The improved Auto-Injector has been introduced in all European countries where Epipen® is approved.

Important identified risk: Accidental injection

Risk minimisation measures
Objective and rationale: • To ensure correct handling of the EpiPen® Auto-Injector and therefore to avoid undesirable effects due to accidental injections. • The Auto-Injector has been newly designed to make handling easier and safer providing a more ergonomic design and a new needle-protection mechanism after use. This will prevent accidental needle sticks and allow for safe disposal of the Auto-Injector. • Educational material is to ensure that healthcare professionals and patients/carers are able to successfully administer the product based on the instructions in the product information.
Summary description of main additional risk minimisation measures: • Educational material includes: - 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.
The improved Auto-Injector has been introduced in all European countries.

Important identified risk: Lack of efficacy due to wrong handling or lack of efficacy when no wrong handling or device failure was reported

Risk minimisation measure
Objective and rationale: • To ensure correct dosage and storage of the EpiPen® Auto-Injector as well as prevention of administration of expired drug and therefore facilitating patients' benefit from treatment. • In the approved SmPC, it is stated that a second injection may be necessary 5-15 minutes after the initial treatment. • Sometimes patients do not know if they have administered the Auto-Injector successfully. The viewing window of the newly designed Auto-Injector serves in addition as a visual indicator that the dose of adrenaline has been delivered. After completed injection the viewing window is obscured. • Educational material is to ensure that healthcare professionals and patients/carers are able to successfully administer the product based on the instructions in the product information.
Summary description of main additional risk minimisation measures: • Educational material includes: - 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.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
PK/PD study: Pharmacokinetic/ Pharmacodynamic (PK/PD) Study to Evaluate	To compare adrenaline PK/absorption (AUC, C_{max}, t_{max}) of intramuscular	Safety concern: Lack of efficacy (when no wrong handling or device failure was	Study planned. Not yet approved.	Study report: 12 months after approval.

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Adrenaline (Epinephrine) Exposure Following Intramuscular Administration of Fastjekt® Auto-Injector (0.3 mg; Mylan) in Adult Volunteers with Varying Skin to Muscle Distance (STMD) in the Thigh	(IM) administration of EpiPen® (Adrenaline) Auto-Injector (0.3 mg) vs standard syringe/needle equipment, at mid-anterolateral thigh in healthy volunteers To compare adrenaline PK/absorption of EpiPen® vs placebo syringe, administered at mid-anterolateral thigh To compare PD parameters: heart rate (HR), systolic/diastolic blood pressure (SBP/DBP)	reported)		

Studies which are a condition of the marketing authorisation

The above mentioned study is no condition of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
02	28 May 2013	Identified Risks: 1. Auto-Injector not working in a critical situation 2. Accidental injection 3. No or reduced effect from injection Potential Risks: None. Missing information: None.	Inclusion on monitoring of effectiveness of EpiPen® educational materials by means of a survey No additional identified or potential risks in comparison to former version.
03	N/A	Identified Risks: 1. Auto-Injector not working in a critical situation 2. Accidental injection 3. No or reduced effect from injection Potential Risks: None. Missing information: None.	Adaption to the new EU-RMP format and update of the post-marketing experience. No additional identified or potential risks in comparison to former version.
04		Identified Risks: 1. Device failure 2. Accidental injection 3. Lack of efficacy due to wrong handling or lack of efficacy when no wrong handling or device failure was reported Potential Risks: 1. Serious allergic reaction to sodium	Update of the RMP according to the BfArM deficiency letter and EMA referral. Educational material, SmPC and PIL were updated according to the Assessment Report. PK/PD study will be

Version	Date	Safety Concerns	Comment
		metabisulfite content of EpiPen® 2. Serious cardiovascular adverse reaction in predisposed patients <u>Missing information:</u> None.	conducted subsequent to approval.