Summary of Risk Management Plan for Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector (Adrenaline Auto-Injector)

This is a summary of the risk management plan (RMP) for Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector. The RMP details important risks of Adrenaline Auto-Injector, how these risks can be minimised, and how more information will be obtained about Adrenaline Auto-Injector's risks and uncertainties (missing information).

Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

Important new concerns or changes to the current ones will be included in updates of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector's RMP.

I. The Medicine and What it is Used For

Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector is authorised for use in the emergency treatment of severe acute allergic reactions (anaphylaxis) to e.g., insect stings or bites, foods, drugs and other allergens, as well as idiopathic or exercise induced anaphylaxis.

Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. It contains adrenaline (epinephrine) as the active substance, and it is given by injection in pre-filled pen (Auto-Injector) 0.3 mg per dose (Epinephrine 0.3 mg/0.3 mL Auto-Injector) and 0.15 mg per dose (Epinephrine 0.15 mg/0.3 mL Auto-Injector).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of Important Risks and Missing Information

Important risks of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.);

Table 13: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
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

II.B Summary of Important Risks

Table 14: Part VI.2- Important Identified Risk – Device failure

Evidence for Linking the Risk to the Medicine	Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector is indicated in the emergency treatment of severe allergic reactions (anaphylaxis). Anaphylaxis represents an important life-threatening medical emergency. Failure of device would hinder adequate treatment and therefore may cause death. Due to the referral procedure under Article 31 of Directive 2001/83/EC, the EMA concluded that the important safety concerns of "device failure" should be included in the RMP. Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimisation measures Additional risk minimisation measures • Educational material

Table 15: Part VI.2- Important Identified Risk – Accidental injection

Evidence for Linking the Risk to the Medicine	Following a referral procedure under Article 31 of Directive 2001/83/EC, the CHMP concluded that accidental injection should be considered as one of the important safety concerns for Adrenaline Auto-Injectors [67]. Accidental epinephrine digital injection by Auto-Injector is a known risk of these dispensing units [68]. In a retrospective review [7], 5,190 needle-stick injuries from adrenaline Auto-Injectors were reported between 1994 and 2007. Overall, 60 % of injuries were reported between 2003 and 2007, and patients experiencing unintentional injection had a median age of 14 years. Due to the potent local vasoconstrictor effect of epinephrine accidental injection into digits, hands or feet may result in peripheral ischemia requiring treatment in some cases. Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Accidental injection occurs either by the patient itself, by health care professionals (HCP) or others when attempting to treat the patient. In some cases, patients or HCPs report that they used expired Auto-Injectors for training which resulted in accidental injection. The design of the Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector provides needle retraction after use as well as complete patient interaction at only one end of the device
Risk Minimisation Measures	Routine risk minimisation measures Additional risk minimisation measures • Educational material

Table 16: Part VI.2- Important Identified Risk – Lack of efficacy (due to wrong handling or lack of efficacy when no wrong handling or device failure was reported)

Evidence for Linking the Risk to the Medicine	Although highly effective, it has been reported that even early and repeated administration of epinephrine does not prevent fatalities in 12 % to 14 % of anaphylactic events [70]. Following a referral procedure under Article 31 of Directive 2001/83/EC, the CHMP concluded that lack of efficacy should be considered as one of the important safety concerns for adrenaline (epinephrine) auto-injectors [67]. Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Lack of efficacy due to wrong handling:
	The Auto-Injectors are used by any age group as well as from patients, caregivers or health care professionals in life threatening and high-stress emergency situations. Therefore, it cannot be reasonably expected that handling errors could be completely avoided/prevented. No specific risk group could be identified. Lack of efficacy when no wrong handling or device failure was reported: Although highly effective, epinephrine does not entirely remove the mortality risk of anaphylaxis. This implies that even after early selfadministration of epinephrine, anaphylaxis may have a fatal outcome. This may be because of a number of different factors, such as patient's constitution and co-morbidities, type and amount of allergen exposure, poor epinephrine absorption (e.g., due to accidental s.c. administration), epinephrine resistance or the need for repeated doses [69].
Minimisation Risk Measures	Routine risk minimisation measures Additional risk minimisation measures • Educational material

Table 17: Part VI.3- Important Potential Risk – Serious allergic reaction to sodium metabisulfite content of Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector

Evidence for Linking the Risk to the Medicine	Sodium metabisulfite is commonly used as a drug preservative, and every commercially available preparation of epinephrine contains sodium metabisulfite [71]. In Adrenaline Auto-Injector, it prevents browning which decreases its effectivenesss [73]. Metabisulfite may rarely cause severe hypersensitivity reactions including anaphylactic symptoms and bronchospasm in susceptible individuals, especially those with a history of asthma. In patients suffering from asthma, metabisulfite can cause severe respiratory symptoms in between 5 and 13 %. According to published data, the incidence of positive patch test results with metabisulfite ranges from 1.4 % to 4 %, but only few authors have been able to prove the true relationship between positive test results and exposure to this allergen [74]. Symptoms of allergic reactions to sodium metabisulfite are bronchospasm, urticaria, angioedema, nausea, abdominal pain, diarrhea, seizures, as well as anaphylactic and anaphylactoid reactions [71] [74]. Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Patients with an allergy to sulphites, susceptible individuals, especially those with a history of asthma.
Risk Minimisation Measures	Routine risk minimisation measures Additional risk minimisation measures
	• Not applicable as there are no additional risk minimisation measures for this safety concern

Table 18: Part VI.3- Important Potential Risk – cardiovascular adverse reaction in predisposed patients

Evidence for Linking the Risk to the Medicine	The potential risk “serious cardiovascular adverse reaction in predisposed patients” was included and discussed in the RMP upon a request of the Germany Health Authority (Federal Institute for Drugs and Medical Devices - BfArM). The development of adverse reactions in one of every five cardiac patients was observed in a prospective, observational study registering 966 indoor cardiology patients by Kaur et al., pointing toward a grave situation [77]. Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.

Risk Factors and Risk Groups	Patients who have a heart disease are at increased risk of adverse reactions. Adrenaline should only be prescribed to those patients, but also those suffering from diabetes, hyperthyroidism, hypertension and elderly individuals if the potential benefit justifies the potential risk. There is a risk of adverse reactions following epinephrine administration in patients with high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia and hypokalaemia. Patients with these conditions must be carefully instructed in regard to the circumstances under which Epinephrine 0.3 mg/0.3 mL and 0.15 mg/0.3 mL Auto-Injector should be used.
Risk Minimisation Measures	Routine risk minimisation measures Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

Not applicable.

II.C.2 Other Studies in Post-Authorisation Development Plan

Not applicable.