Part VI: Summary of the risk management plan

VI.1 Summary of risk management plan for Emerade® (adrenalin)

This is a summary of the risk management plan (RMP) for Emerade®. The RMP details important risks of Emerade®, how these risks can be minimised, and how more information will be obtained about Emerade® 's risks and uncertainties (missing information).

Emerade®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Emerade® should be used.

Important new concerns or changes to the current ones will be included in updates of Emerade's RMP.

I. The medicine and what it is used for

Emerade® is authorised for the indication of the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

It contains adrenalin as the active substance, and it is given as an intramuscular (i.m.) injection only on the outer thigh.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Emerade®, together with measures to minimise such risks and the proposed studies for learning more about Emerade® 's 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 — only one or two Emerade® pens are in the box. Amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — Emerade® is only available as a prescription drug

Together, these measures constitute routine risk minimisation measures.

In the case of Emerade®, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including the Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Emerade® not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Emerade® are risks that need special risk management activities to investigate further or minimise the risk so that the medicinal product can be safely administered. 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 Emerade®. 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)

Important identified risks*	• Drug administration error including accidental injection
	• Lack of drug effect
	• Auto-injector not working in a critical situation:
	  ○ Failure to discharge (Needle blockage, e.g., waxy ester/rust)
	  ○ The failure to activate

Important potential risks	None
Missing information	Use during pregnancy

**Based on MHRA Preliminary Variation Assessment Report (CMDh/205/2005 Rev.4) as Concerned Member State (CMS) comments, the important identified risks have been separated.*

II.B Summary of important risks

Important identified risk **Drug administration error including accidental injection**	
Evidence for linking the risk to the medicine	SmPC, Post-marketing, Literature and Clinical Trial data

Risk factors and risk groups	Factors associated with: • Patients who do not follow the instructions for the use of the product • Patient characteristics (e.g., personality, literacy and language barriers) • Labelling and packaging.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • Mentioned in section 4.2 of the SmPC • Mentioned in section 4.4 of the SmPC • Mentioned in section 4.9 of the SmPC • A clear method of administration together with pictogram is mentioned in section 6.6 of the SmPC • Prescription-only medicine (POM) • Package design <u>Additional risk minimisation measures:</u> Educational materials: • Prescriber checklist • Patient Brochure • Training device • Websites with Video-Audio materials

Important identified risk **Lack of drug effect**	
Evidence for linking the risk to the medicine	SmPC, Post-marketing, Literature and Clinical Trial data
Risk factors and risk groups	Factors associated with:

	• Patients who do not follow the instructions for the use of the product • Patient characteristics (e.g., personality, literacy and Misconception).
Risk minimisation measures	Routine risk minimisation measures: • Mentioned in section 4.2 of the SmPC • Mentioned in section 6.6 of the SmPC • Prescription-only medicine (POM) Additional risk minimisation measures: • Prescriber checklist • Patient Brochure • Training device • Websites with Video-Audio materials
Additional pharmacovigilance activities	A new PK/PD study #905

Important identified risk **Auto-injector not working in a critical situation** • **Failure to discharge (Needle blockage, e.g., waxy ester/rust)** • **The failure to activate**	
Evidence for linking the risk to the medicine	SmPC, Post-marketing, Literature and Clinical Trial data
Risk factors and risk groups	Factors associated with usage of the product (Patients who do not use the product correctly). Factors associated with quality of the product: • Needle blockage, injection of particles and presence of corrosion–based obstructions within the cannula lumen, and failure to activate which can prevent the Emerade® pen to activate • Patients have to carry the Emerade® around by all times, which may result in the exposure of the product to temperatures that exceed the labelled storage conditions as described on the patient

	information leaflet (below 25°C). It is possible that under temperature excursions, which are cumulative in terms of component creep, the product may fail to activate.
Risk minimisation measures	Routine risk minimisation measures: • Mentioned in section 4.8 Undesirable effects of the SmPC • The detailed method of administration is mentioned in section 6.6 of the SmPC • Prescription-only medicine (POM) Additional risk minimisation measures: • Prescriber checklist • Patient Brochure • Training device • Video-Audio materials

Missing information **Use during pregnancy**	
Risk minimisation measures	Routine risk minimisation measures: • Mentioned in section 4.6 of the SmPC • Prescription-only medicine (POM) Additional risk minimisation measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Emerade®.

II.C.2 Other studies in post-authorisation development plan

Planned additional pharmacovigilance activities.

Category 3 - Required additional pharmacovigilance activities by the competent authority				
Study (study short name, and title) Status (planned)	Summary of objectives	Safety concerns addressed *(list)*	Milestones (required by regulators)	Due dates (in DD/MM/YYYY format)
An open label, 6-period, 3-sequence, 3-treatment, cross-over study to investigate the pharmacokinetics and pharmacodynamics of epinephrine following administration of two different doses of Emerade auto-injector and the same doses by manual intramuscular injection in subjects with varying body masses and skin-to-muscle-depths of the thigh. Planned	1- To investigate and compare the PK/PD of epinephrine following Emerade auto-injector and manual IM epinephrine injection at two dosing levels in a cross-over manner 2- To determine the relationships between body mass (i.e., weight in kg) and the PK and PD of epinephrine following Emerade and IM epinephrine injection 3- To determine the relationships between compressed skin-to-muscle-depth in the thigh (STMD) and the PK and PD of epinephrine following Emerade and an IM epinephrine injection. 4- Exploratory: To determine additional PD parameters (e.g cardiac output, stroke volume)	lack of drug effect	Protocol submission:	13/Nov/2020 within variation SE/H/1261/01-03/II/26
			Final report planned	It estimated 12 months after study approval. Timelines may be subject to prolongation due to the COVID- 19 pandemics and its impact on study conduct at sites that are specialized in the conduct of PK/PD studies.

	that could be used to determine the potential for efficacy of epinephrine.			