SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Emerade, 500 micrograms, solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The pre-filled pen contains 0.5 ml of adrenaline solution 1 mg/ml.

Emerade 500 micrograms delivers a single dose of 0.5 ml containing 500 micrograms of adrenaline (as tartrate).

Each 0.5 ml (500 micrograms) dose contains 0.25 mg sodium meta-bisulphite (E223).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen (auto-injector).
Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Emerade is indicated for 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.

4.2 Posology and method of administration

Posology
The effective dose is usually within the range 5- 10 micrograms per kg bodyweight but higher doses may be necessary in some cases.

Paediatric population
Use in children: Emerade 500 micrograms is not recommended for use in children.

Children below 15 kg bodyweight
A dosage below 150 micrograms cannot be administered with sufficient accuracy in children weighing less than 15 kg and use is therefore not recommended unless during a life-threatening situation and under medical advice.
Children between 15 kg and 30 kg bodyweight
The usual dose is 150 micrograms.

Children over 30 kg bodyweight
The usual dose is 300 micrograms.

Adolescent patients over 30 kg bodyweight
The dosage recommendations for adult patients should be followed.

Adults
The recommended dose is 300 micrograms for individuals under 60 kg bodyweight. The recommended dose is 300 to 500 micrograms for individuals over 60 kg bodyweight, depending on clinical judgement.

An initial dose should be administered as soon as symptoms of anaphylaxis are recognised.

Method of administration

Emerade is intended for intramuscular administration of adrenaline.

For single use.

Emerade should be administered early, at the first signs of anaphylaxis. A poor outcome from anaphylaxis is associated with late administration of adrenaline.
Emerade must be injected in the outer side of the thigh.
Massaging around the injection area accelerates absorption.
The injection can be administered through clothing.

The patient/carer should be informed that following each use of Emerade:

- They should call for immediate medical assistance, ask for an ambulance and state 'anaphylaxis' **even if symptoms appear to be improving (see section 4.4)**.
- Conscious patients should preferably lie flat with feet elevated but sit up if they have breathing difficulties. Unconscious patients should be placed on their side in the recovery position.
- The patient should if possible remain with another person until medical assistance arrives.
- If the patient still feels unwell after the first injection, a second injection should be administered 5-15 minutes after the first injection.
- It is recommended that patients are prescribed two Emerade pens which they should carry at all times.

For detailed instruction for use, refer to section 6.6.

4.3 Contraindications

There are no absolute contraindications to the use of Emerade in an allergic emergency.

4.4 Special warnings and precautions for use

Do not remove the cap until ready for use.
Emerade must be administrated only into the anterolateral thigh.
The injection is delivered immediately after the triggering cylinder is pressed against the skin.
Patients should be advised not to inject Emerade into the *gluteus maximus* due to the risk of accidental injection into a vein.

Emerade should be used in emergency situations as life-sustaining treatment.

The patient must urgently seek medical assistance for further treatment after using Emerade.

All patients who are prescribed Emerade should be thoroughly instructed to understand the indications for the use and the correct method of administration (see section 6.6). It is strongly advised also to educate the patient's immediate associates (e.g. parents, caregivers, teachers) for the correct usage of Emerade in case support is needed in the emergency situation.

The patient/carer should be informed about the possibility of biphasic anaphylaxis which is characterised by initial resolution followed by recurrence of symptoms some hours later. Patients with concomitant asthma may be at increased risk of a severe anaphylactic reaction.

Use with caution in patients with heart diseases including angina pectoris, cardiac arrhythmia, *cor pulmonale*, obstructive cardiomyopathy and atherosclerosis. There is also a risk for adverse reactions after the administration of adrenaline to patients with hyperthyroidism, hypertension, phaeochromocytoma, glaucoma, severe renal impairment, prostate adenoma, hypercalcaemia, hypokalaemia, diabetes, and in elderly patients and pregnant women.

In patients with a thick sub-cutaneous fat layer, there is a risk of adrenaline being administered in the sub-cutaneous tissue which may result in a slower adrenaline absorption (see section 5.2) and a suboptimal effect. This may increase the need for a second Emerade injection (see section 4.2).

Unintentional injection in hands and feet can result in peripheral ischemia that may require treatment.

Patients should be warned regarding related allergens and should be investigated whenever possible so that their specific allergens can be characterised.

Emerade contains sodium metabisulphite
Sodium metabisulphite may rarely cause severe hypersensitivity reactions including anaphylaxis and bronchospasm in sensitive individuals particularly in those with a history of asthma. All those patients should be carefully instructed in which circumstances Emerade must be used.

Emerade contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Certain medicines can enhance the effect of adrenaline: Tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and catechol-O-methyl transferase (COMT) inhibitors. Adrenaline must be used with caution in patients receiving halogenated hydrocarbons and related medicines and drugs that may sensitize the heart to arrhythmias, e.g. digitalis, quinidine, halogenated anaesthetics.

The administration of fast-acting vasodilators or α-blockers can counteract the effects of adrenaline on blood pressure. β-blockers can inhibit the stimulating effect of adrenaline.

The hyperglycaemic effect of adrenaline may necessitate an increase in insulin or oral hypoglycaemic treatment in diabetic patients.

4.6 Fertility, Pregnancy and lactation

There are no adequate or well-controlled studies of adrenaline during pregnancy. Adrenaline should be used in pregnancy only when the potential benefit to the mother outweighs the possible risk to the foetus.

Because of its poor oral bioavailability and short half-life, any adrenaline in breast milk is unlikely to affect the nursing infant.

4.7 Effects on ability to drive and use machines

Emerade has no or negligible influence on the ability to drive and use machines, however, patients are not recommended to drive or use machines following administration of adrenaline, since they will be affected by the anaphylactic reaction.

4.8 Undesirable effects

Side-effects of adrenaline in general are associated with the α- and β-receptor activity of adrenaline.
The following table is based upon experience with the use of adrenaline.

The adverse events were classified according to the following frequencies: Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Metabolic and nutrition disorders	Not known	Hyperglycaemia, hypokalaemia, acidosis
Psychiatric disorders	Not known	Anxiety, hallucination
Nervous system disorders	Not known	Headache, dizziness, tremor, syncope
Cardiac disorders	Not known	Tachycardia, arrhythmia, palpitations, angina pectoris, stress cardiomyopathy
Vascular disorders	Not known	Hypertension, vasoconstriction, peripheral ischaemia
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm
Gastrointestinal	Not known	Nausea, vomiting

disorders		
General disorders and administration site conditions	Not known	Hyperhidrosis, asthenia

Emerade contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom

Yellow Card Scheme; Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Any pen that is suspected of not having functioned as intended should be retained for reporting and investigation. Such pens should eb returned to your/the nearest pharmacy.

4.9 Overdose

An overdose, or an accidental intravascular injection of adrenaline, can originate a sudden increase in blood pressure that can cause cerebral haemorrhage. Severe pulmonary oedema caused by peripheral vasoconstriction together with cardiac stimulation can result in death. Severe pulmonary oedema with difficulty in breathing can be treated with fast-acting α-blockers. Life-threatening heart arrhythmias can be treated with β-blocking agents.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac stimulants excl. cardiac glycosides - Adrenergic and dopaminergic agents – Adrenaline, ATC-code: C01CA24

Adrenaline is the natural active sympathomimetic hormone from the adrenal medulla. It stimulates both the α- and β-adrenergic receptors. Adrenaline is the first choice for emergency treatment of severe allergic reactions and idiopathic or exercised-induced anaphylaxis.

Adrenaline has a potent vasoconstrictive effect through its α-adrenergic stimulation. This effect counteracts the vasodilatation and increased vascular perfusion, leading to

low intravascular flow and hypotension, which are the main pharmacotoxicological effects in the anaphylactic shock.

By stimulating β-receptors in the lungs, adrenaline produces a potent bronchodilator effect with relief of wheezing and dyspnea. Adrenaline also relieves pruritus, urticaria and angioedema associated to anaphylaxis.

5.2 Pharmacokinetic properties

Circulating adrenaline is metabolized in the liver and other tissues by the enzymes COMT and MAO. Inactive metabolites are excreted in the urine.

The half-life of adrenaline in plasma is about 2 to 3 minutes. However, when adrenaline is injected subcutaneously or intramuscularly the absorption is retarded by local vasoconstriction and thus the effects can last longer than as predicted by half-life. Massage around the injection site is advised to accelerate absorption.

In a comparative PK/PD study in healthy subjects of Emerade 300 mcg with other marketed adrenaline auto-injectors in the same strength but with shorter needles and higher propulsive force, an influence of propulsive force upon plasma adrenaline concentrations was indicated. Despite high variability in plasma adrenaline concentrations, devices with shorter needles demonstrated a trend to superior adrenaline bioavailability in the time critical first 30 minutes following injection, compared with Emerade. Therefore, despite a longer needle, plasma adrenaline concentrations appear to be lower following Emerade compared with devices that have shorter needles but higher propulsive force. The reasons for this are not understood but it underlines the importance of carrying two Emerade devices at all times.
A within-product (Emerade) comparative analysis was also conducted in healthy subjects with different STMD. In Cohort 1 (STMD ≥ 10, <15 mm) mean adrenaline concentrations displayed two peaks. An initial early peak was observed in the first 5 minutes, and a second peak was observed between 40 and 60 minutes. Concentrations in the initial peak were generally lower than concentrations in the second peak. A similar early peak could be observed for adrenaline concentrations following Emerade 300 μg or Emerade 500 μg in Cohorts 2 (STMD ≥ 15, ≤ 20 mm) and 3, (STMD > 20 mm) although the initial peak was not as pronounced as in the first cohort. After Emerade 500 μg injection, adrenaline concentrations in Cohort 2 rapidly increased to a plateau around 8 minutes. The concentrations remained at this value steadily up to about 30 minutes, and then decreased for the remainder of the measured timepoints.

Due to the high variability of adrenaline plasma concentration observed in the conducted PK/PD studies, robust conclusions cannot be drawn.

Adrenaline bioavailability in healthy subjects who have well perfused subcutaneous tissue cannot necessarily be extrapolated to patients in established anaphylactic shock in whom there may be peripheral circulatory shutdown. This underlines the importance of early administration of adrenaline at the first signs of anaphylaxis, while the superficial tissues are still well perfused, in order to maximise adrenaline uptake into the systemic circulation.

5.3 Preclinical safety data

Adrenaline has been extensively used in the emergency treatment of severe allergic reactions for many years. There is no further preclinical data relevant for prescribers besides those already described in this SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium meta-bisulfite (E223)

Disodium edetate

Hydrochloric acid (for adjustment of pH)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Emerade 150 micrograms: 18 months
Emerade 300 micrograms and Emerade 500 micrograms: 2 years

6.4 Special precautions for storage

Store in plastic, protective case provided. The plastic case containing the pen/pens can be kept in the outer carton.

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Emerade consists of a pre-filled syringe made of glass with a polyisoprene rubber needle plunger in an auto-injector. Emerade is latex free.

Exposed needle length
Emerade 150 micrograms: 16 mm
Emerade 300 micrograms and Emerade 500 micrograms: 23 mm

Package
Emerade has an outer carton as well as a plastic carton to store the auto-injector in.
Pack sizes: 1 or 2 pre-filled pens.

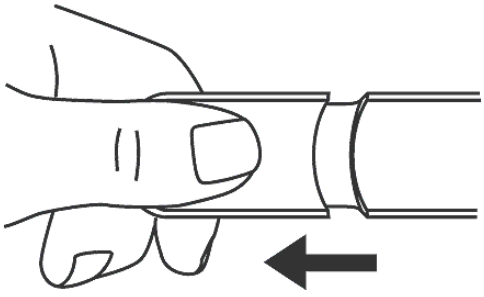
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

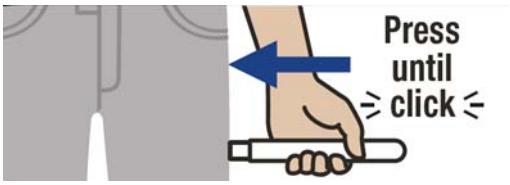
It is very important that the patient receives detailed information on how to use Emerade.

For single use only.
The expiry date is indicated on the label and on the outer carton and Emerade should not be used after this date.
Discard and replace the auto-injector after expiry date.
Check the solution periodically through the inspection window of the unit by lifting the label to make sure the solution is clear and colourless. Discard and replace Emerade if the solution is discoloured or contains particles.
Emerade should always be carried if at risk of anaphylaxis.

Method of administration
The instructions for use must be carefully followed in order to avoid accidental injection.
It is recommended that your family members, carers or teachers are also instructed in the correct use of Emerade.
Emerade is designed for easy use and has to be considered as a first aid. Emerade should be administered early, at the first signs of anaphylaxis. Emerade is intended for intramuscular administration of adrenaline. Emerade must be injected in the outer side of the thigh and the injection occurs when the triggering cylinder is firmly pressed into the thigh. The injection can be administered through clothing. Massaging around the injection area accelerates absorption.
Emerade has an opening only at the needle end and none at the opposite end.

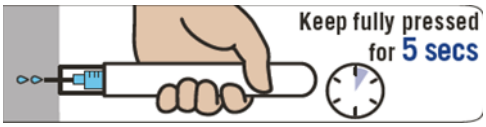


1. Remove the cap.



2. Place Emerade against the outer side of the thigh at a 90° angle and press firmly so that the needle cover is depressed. A click can be heard when the device has activated and the needle has penetrated the thigh.

and



Hold Emerade fully pressed against the thigh for 5 seconds. Lightly massage the injection site afterwards.

3. Seek immediate medical help.

The needle in Emerade is protected before, during and after the injection.
When the injection is completed, the needle cover of the Emerade pen is visibly longer and the plunger is visible in the inspection window by lifting the label.

After using of Emerade pen following the instructions, the patient can verify if the pen is activated. Pictures below (Fig.1-Fig.2) apply to all doses of Emerade (150 micrograms, 300 micrograms and 500 micrograms).

The unused Emerade pen (before activation) has needle cover in its normal position (Fig. 1).

Fig.1

Emerade pen that has been activated, will have an extended needle cover (Fig. 2).

Fig.2

If the needle cover has not extended, the pen has not activated.

An Emerade pen that has activated, and has successfully delivered a dose of adrenaline, will show a coloured plunger in the inspection window (revealed by peeling back the label on the pen):

150 micrograms: yellow
300 micrograms: green
500 micrograms: blue.

If the inspection window still shows clear liquid (adrenaline solution), the pen has not successfully delivered a dose of adrenaline. The arrow on the pen label indicates where the label can be lifted up in order to reveal the inspection window.

If an Emerade adrenaline pen fails to activate immediately, an additional attempt should be made using an increased force when pressing the pen against the intended injection site. If not successful proceed to immediately to use your second pen.

Sometimes a single dose of adrenaline may not be sufficient to completely reverse the effects of a serious allergic reaction. For this reason, your doctor is likely to prescribe two Emerade pens for you. If your symptoms have not improved or have deteriorated within 5-15 minutes after the first injection, either you or the person with you should give a second injection. For this reason you should carry two Emerade pens with you at all times.

Emerade is intended only for emergency treatment. You must always contact your doctor or go to the nearest hospital for further treatment. Inform your doctor that you have taken an injection of adrenaline. Take the used auto-injector with you.

See Section 4.2 for instructions to be conveyed to the patient/carer regarding actions to be taken following each use of Emerade.

Do not remove the cap unless injection is required.
Some liquid remains in the auto-injector after the injection. The auto-injector cannot be re-used.

Discard Emerade in accordance with local requirements.

Instructions for use are shown on the label, package and package leaflet.

Autoinjectors without needles are available for training purposes.

7 MARKETING AUTHORISATION HOLDER

PharmaSwiss Česká republika s.r.o.
Jankovcova 1569/2c
170 00 Prague 7
Czech Republic

8 MARKETING AUTHORISATION NUMBER(S)

PL 33616/0015

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