SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Emerade 150 mcg
Emerade 300 mcg
Emerade 500 mcg

Solution for injection, Intramuscular

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Emerade 150 mcg delivers a single dose of 0.15 ml containing 150 micrograms of epinephrine tartrate.
Emerade 300 mcg delivers a single dose of 0.3 ml containing 300 micrograms of epinephrine tartrate.
Emerade 500 mcg delivers a single dose of 0.5 ml containing 500 micrograms of epinephrine tartrate.

Each 0.15 ml (150 micrograms) dose contains 0.075 mg sodium meta-bisulphite (E223).
Each 0.3 ml (300 micrograms) dose contains 0.15 mg sodium meta-bisulphite (E223).
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 in the emergency treatment of severe allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.
Emerade is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.
Emerade is intended for immediate administration as emergency supportive therapy only and is not a substitute for immediate medical care.

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 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.

Use in 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. In the absence of clinical improvement or if deterioration occurs, a second injection with an additional Emerade may be administered 5 – 15 minutes after the first injection. It is recommended that the patients are prescribed two Emerade pens which they should carry at all times.

Method of administration

For intramuscular injection only.
For single use.

Emerade is given intramuscularly as soon as the symptoms of anaphylactic shock arise. 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.

For detailed instruction for use, refer to section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions 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.

Emerade contains sodium metabisulphite which can cause allergic 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.

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 is essentially sodium free (contains less than 1 mmol sodium (23 mg) per dose).

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 disorders	Not known	Nausea, vomiting
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

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.

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

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

The pen must always be kept in the plastic case provided to ensure it is protected.
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 black chlorobutyl rubber stopper 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 a plastic box as well as an outer carton boxbox to store the auto-injector in.
Pack sizes: 1 or 2 pre-filled pens.

Not all pack sizes may be marketed.

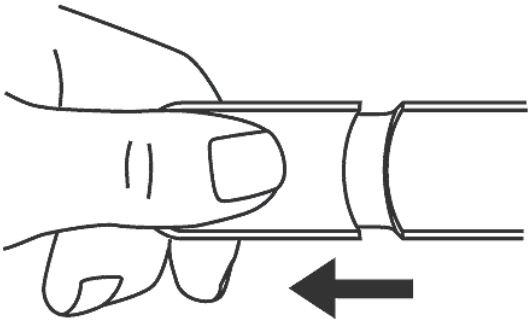
6.6 Special precautions for disposal and other handling

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

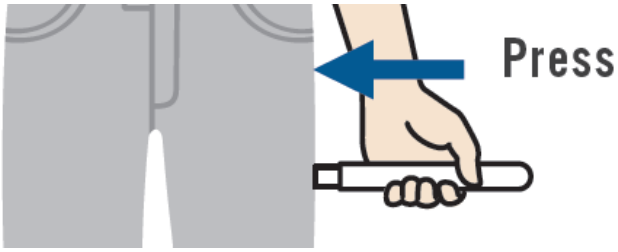
For single use only.
The expiry date is indicated on the label and on the outer carton and Emerade should not be used after this date.
Discard and replace the auto-injector after expiry date.
The solution should be checked periodically through the inspection window of the unit by lifting the label to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

Emerade is designed for easy use and has to be considered as a first aid. Emerade has an opening only at the needle end and none at the opposite end.

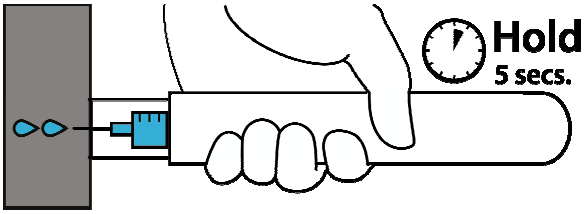
Method of administration
The instructions for use must be carefully followed in order to avoid accidental injection.
It is recommended that the patient's family members, carers or teachers are also instructed in the correct use of Emerade.
Emerade should only be used for injection in the outer thigh. The injection occurs when Emerade is pressed into the thigh. This can be done through clothing.



1. The needle shield should be removed



2. Emerade should be placed and pressed against the outer side of the thigh. A click can be heard when the injection goes into the muscle.



3. Emerade should be held against the thigh for about 5 seconds. The injection site should be lightly massaged afterwards.

   The patient should be instructed to seek immediate medical help.

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

Sometimes a single dose of adrenaline may not be sufficient to completely reverse the effects of a serious allergic reaction. If the symptoms have not improved or have deteriorated within 5-15 minutes after the first injection, either the patient or the person with him should be instructed to give a second injection. For this reason, the patient should be instructed to carry more than one Emerade with him at all times.

Autoinjectors without needles are available for training purposes.

7. MANUFACTURER

Rechon Life Science AB
P.O.B 60043, SE-216 13 Llimhamn, Sweden
For Valeant Pharmaceuticals, Ireland

8. MARKETING AUTHORISATION HOLDER

Neopharm Ltd.
Hashiloach 6. POB 7063,
Petach-Tikva 4917001
Israel

9. MARKETING AUTHORISATION NUMBER(S)

Emerade 150 mcg 35660
Emerade 300 mcg 35661
Emerade 500 mcgs 35727

The content of this leaflet was approved by the Ministry of Health in December 2019 and updated according to the guidelines of the Ministry of Health in February 2020