# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Adrenaline Accord 0,1 mg/ml, oplossing voor injectie in een voorgevulde spuit

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 0.1 mg epinephrine (adrenaline).

Each 10 ml pre-filled syringe contains 1 mg epinephrine (adrenaline).

Excipient with known effect:
Sodium metabisulphite 0.46 mg per ml (E223)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

A clear, colourless solution

pH: between 2.3 to 4.0

Osmolality of the solution: 260-320 mOsmol/kg

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Cardiopulmonary resuscitation in adults and children ≥ 20 kg body weight
- Acute anaphylaxis in adults

### 4.2. Posology and method of administration

**Posology**
Intravenous or intraosseous adrenaline should only be administered by those experienced in the use and titration of vasopressors in their normal clinical practice.

Cardiopulmonary resuscitation:

*Adults*
1 mg using intravenous boluses every 3-5 minutes.
If the drug is injected via a peripheral vein catheter, the drug must be flushed out with at least 20 mL of 0.9% sodium chloride for injection (to facilitate entry into the central circulation).
If venous access is not available, intraosseous administration of the same dosage is recommended.

*Paediatric population (≥ 20 kg body weight)*
0.01 mg/kg using intravenous boluses. Maximum single dose is 1 mg. Subsequent doses of adrenaline may be given every 3–5 min. If venous access is not available, intraosseous administration of the same dosage is recommended.

Acute anaphylaxis

The equipment for the treatment of anaphylactic shock must be very clearly distinguished between 0.1 mg/ml and 1 mg/ml of adrenaline solution. Adrenaline 0.1 mg/ml solution for injection in pre-filled syringe is not recommended for intramuscular use in acute anaphylaxis. For intramuscular administration in anaphylaxis, a 1 mg/ml solution should be used.

It is important that time is not wasted in attempting to find intravenous line if intramuscular injection may still be possible.

In the treatment of anaphylaxis, adrenaline for intravenous administration should only be administered by experienced personnel under the observation of heart rate and blood pressure. The 0.1 mg/ml solution of adrenaline is given to adults as 0.05 mg iv bolus dose and titrated in increments of boluses of 0.05 mg according to response.

This medicinal product is not appropriate to deliver a dose of less than 2 ml and should therefore not be used in paediatric patients.

*Elderly*
The safety and efficacy of epinephrine (adrenaline) in age categories of elderly patients have not been well established. Dosing selection should be cautious for elderly patients who may be more sensitive for adverse events.

## 4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1. See section 4.4 for additional information regarding sulfites.

## 4.4 Special warnings and precautions for use

<Invented name> is indicated for emergency treatment. Medical supervision is necessary after administration. Intravenous adrenaline should only be used by those experienced in the use and titration of vasopressors in their normal clinical practice.
For intramuscular administration in anphylaxis, a 1 mg/ml solution should be used.

<Invented name> should be used with caution in patients with cardiovascular diseases including angina pectoris, obstructive cardiomyopathy, cardiac arrhythmia, cor pulmonale, atherosclerosis , coronary insufficiency, structural cardiac disease and hypertension due to an increased risk of adverse events following administration.

Patients who receive intravenous epinephrine require continuous monitoring, minimum by ECG, pulse oximetry and frequent blood pressure measurements.

<Invented name> should also be used with caution in patients with hyperthyroidism, pheochromocytoma, narrow-angle glaucoma, severe renal impairment, prostatic hyperplasia that causes residual urine, hypercalcaemia, hypokalaemia and diabetes.

The risk of toxicity is increased if the following conditions are pre-existing:

- Cerebrovascular disease, organic brain damage or arteriosclerosis
- Patients taking Monoamine oxidase (MAO) inhibitors (see section 4.5)
- Patients taking concomitant medication which results in additive effects, or sensitizes the myocardium to the actions of sympathomimetic agents (see section 4.5).

<Invented name> should be used with caution in pregnant patients.

The effect of beta-agonists can be completely or partially inhibited by concomitant administration of non-selective beta-blockers.

Sodium metabisulphite
This medicine contains less than 1 mmol sodium (23 mg) per ml solution for injection, that is to say essentially ‘sodium- free’.

<Invented name> contains sodium metabisulphite that may rarely cause sever hypersensitivity reactions and bronchospasm.

*Elderly*
<Invented name> should be used cautiously in elderly patients who may be more sensitive to adverse events.

## 4.5. Interaction with other medicinal products and other forms of interaction

Adrenaline should be used with caution in patients treated with medicinal products that can trigger arrhythmias, including digitalis and quinidine.

*Beta-blockers*
Severe hypertension and reflex bradycardia may occur with non-cardioselective beta-blocking agents. Beta-blockers, especially non-cardioselective agents, also antagonise the cardiac and bronchodilator effects of adrenaline.

*Inhalation anesthetics*
Adrenaline injected under anesthesia with volatile halogen can induce severe (ventricular) arrhythmias

*Monoamine oxidase (MAO) inhibitors*
MAO inhibitors may potentiate the effect of adrenaline, use with caution is recommended.

*Tricyclic antidepressants*Normal dosage of tricyclic antidepressants have shown to increase the adrenaline pressor action by 2-3 fold in acute administration of adrenaline at high doses iv. Prolonged hypertension has been observed following 0.5 mg adrenaline subcutaneously in a person treated with protriptyline.

*Alpha-adrenergic blocking agents*
Alpha-blockers antagonise the vasoconstriction and hypertension effects of adrenaline, increasing the risk of hypotension and tachycardia.

*Insulin or oral hypoglycaemic agents*
Adrenaline inhibits the secretion of insulin, thus increasing blood sugar levels. For people with diabetes, it may be necessary to increase their dosage of insulin or oral hypoglycaemic drugs when treated with adrenaline.

*Catechol-O-methyltransferase (COMT) inhibitors*
Drugs containing catechol-O-methyltransferase (COMT) inhibitors (eg. Entacapone, tolcapone) may potentiate the effects of adrenaline.

## 4.6. Fertility, pregnancy and lactation

Pregnancy
Clinical experience in the treatment of pregnant is limited. Data from animal studies are insufficient.

Adrenaline usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labour. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with haemorrhage. If used during pregnancy, adrenaline may cause anoxia to the foetus. For this reason parenteral adrenaline should not be used during the second stage of labour. Adrenaline should only be used during pregnancy if the potential benefits justify the possible risks to the foetus.

Breast-feeding

Adrenaline is distributed into breast milk. Breast-feeding should be avoided by mothers receiving adrenaline.

Fertility
There are no animal studies with respect to effect on fertility.

### 4.7. Effects on ability to drive and use machines

Not relevant under normal conditions of use.

### 4.8. Undesirable effects

The side effects of adrenaline are related to the stimulation of both alpha- and beta- adrenergic receptors.

Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000), not known (cannot be estimated from the available data)

| **System organ class** | Undesirable effects (Frequency unknown) |
|---|---|
| **Metabolism and nutrition disorders** | hypokalaemia, metabolic acidosis, hyperglycaemia |
| **Psychiatric disorders** | anxiety, fear |
| **Nervous system disorders** | headache, dizziness, tremor, paraesthesia, cerebral haemorrhage, syncope |
| **Cardiac disorders** | palpitation, tachycardia, angina pectoris, ventricular arrhythmias, atrial fibrillation, ventricular fibrillation, cardiac arrest, acute myocardial infarction, stress cardiomyopathy |
| **Vascular disorders** | hypertension, coldness of limbs, pallor, vasoconstriction |
| **Respiratory, thoracic and mediastinal disorders** | dyspnea, pulmonary oedema |
| **Gastrointestinal disorders** | nausea, vomiting |
| **General disorders and administration site conditions** | sweating, weakness |

In patients with Parkinsonism, adrenaline can increase rigidity and tremor.

Subarachnoid haemorrhage and hemiplegia have resulted from adrenaline induced hypertension.

Repeated injections can cause necrosis as a result of vascular constriction at the injection site.

**Paediatric population**
Clinical experience suggests a safety profile similar with that of adults.

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 to via the national reporting system listed in Appendix V.

### 4.9 Overdose

*Symptoms of overdose*: In moderate dose; agitation, anxiety, tremor, headache, tachycardia, palpitations, pallor, cold sweat, nausea, vomiting. At high dose;, mydriasis, increase in blood pressure, ventricular arrhythmias, heart failure, pulmonary edema.

*Treatment*: ECG monitoring. In pronounced sinus tachycardia and ventricular arrhythmias, propranolol (for asthmatics rather metoprolol, alternatively atenolol). Alternatively lidocaine in ventricular arrhythmia. At alpha-adrenergic symptoms (such as vasospasm, hypertension) phentolamine as required. Alternatively

glyceryl trinitrate sublingually in repeated doses or intravenous infusion until the desired effect is achieved. Furosemide in pulmonary edema. Otherwise symptomatic therapy.

*Toxicity*: Deactivated in the gastrointestinal tract, inhalation may cause systemic effects. Lowest lethal dose stated as 4 mg, however in general 7-8 mg. 4 mg subcutaneously to 12-year old resulted in severe intoxication. In adult 3 mg subcutaneously resulted in moderate intoxication, 16 mg subcutaneously in severe intoxication and 30 mg intravenously administered for 1 minute very severe intoxication. 50 mg intravenously to 2-year old resulted in irreversible renal failure.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline, ATC code: C01CA24

Mechanism of action
Adrenaline is a direct acting sympathomimetic agent, which exerts effects on both α- and β-receptors.
It has less selectivity between α1- and α2-receptors, and a more pronounced selectivity on β2 compared to β1.

Pharmacodynamic effects
The main effects include increased systolic blood pressure, decreased diastolic blood pressure, tachycardia, hyperglycemia and hypokalemia.

### 5.2 Pharmacokinetic properties

Absorption
Pharmacologically active concentrations of adrenaline is not achieved after oral administration as adrenaline is rapidly oxidized and conjugated in the gastrointestinal mucosa and liver. Absorption from subcutaneous and intramuscular tissue is slow due to local vasoconstriction. Absorption is more rapid after intramuscular injection than after subcutaneous injection.

Distribution
Adrenaline is approximately bound to plasma proteins by 20–30 %.

Adrenaline is rapidly distributed into the heart, spleen, several glandular tissues and adrenergic nerves. It readily crosses the placenta.

Biotransformation
Adrenaline is rapidly inactivated in the body, mostly by the enzymes catechol-O-methyltransferase (COMT).

Elimination
Most of a dose of adrenaline is excreted as metabolites in urine. After intravenous administration, the plasma half-life is approximately 2 to 3 minutes.
Only small amounts are excreted unchanged.

Linearity
In patients with septic shock, adrenaline displays dose-proportional pharmacokinetics in the infusion dose range of 0.026-1.67 µg/kg/min.

*Special populations*
Pharmacokinetic data in patients with hepatic or renal impairment are missing. Pharmacokinetic data with regard to sex and race, are not available.

*Elderly*

In a pharmacokinetic study of 45-minute adrenaline infusions given to healthy men aged 20 to 25 years and healthy men aged 60 to 65 years, the mean plasma metabolic clearance rate of adrenaline at steady state was greater among the older men (144.8 versus 78 mL/kg/min for a 0.0143 mcg/kg/min infusion).

*Body weight*
Body weight has been found to influence adrenaline pharmacokinetics. Higher body weight was associated with a higher plasma epinephrine clearance and a lower concentration plateau.

*Paediatric population*
Pharmacokinetic data in children are limited.

### 5.3 Preclinical safety data

Adrenaline showed negative results for micronucleus assays, sperm abnormality assays and the Ames salmonella assay. However, genotoxic studies (among others Ames tests, mouse lymphoma assay, micronucleus studies) resulted in contradicting results, with positive as well as negative outcomes.

In animal reproduction studies, adrenaline demonstrated adverse developmental effects when administered to pregnant rabbits (gastroschisis), mice (teratogenic effects, embryonic lethality, and delayed skeletal ossification), and hamsters (embryonic lethality and delayed skeletal ossification) during organogenesis at doses approximately 15 times, 3 times and 2 times, respectively, the maximum recommended daily intramuscular or subcutaneous dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Sodium metabisulphite [E223]
Citric acid [E330]
Sodium citrate [E331(iii)]
Water for injection

### 6.2 Incompatibilities

In compatibility studies, this medicinal product has shown to be compatible with 0.9% sodium chloride.

### 6.3 Shelf life

18 months.

### 6.4 Special precautions for storage

Store below 30°C.

### 6.5 Nature and contents of container

10 ml clear pre-filled syringe is composed of clear glass cylinder barrel (type I) having graduation marking per 0.5 ml in blue color with grey thermoplastic elastomer tip cap with grey bromobutyl plunger stopper and polypropylene plunger rod. The glass pre-filled syringe is packed in outer carton box or twist box.

Pack size: 1 pre-filled syringe in outer carton
1 pre-filled syringe in twist box

Not all pack size may be marketed

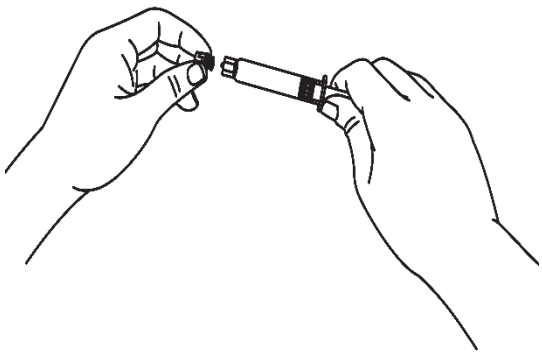
### 6.6 Special precautions for disposal and other handling

The pre-filled syringe is for single patient use only. Discard the syringe after use. Do not reuse.

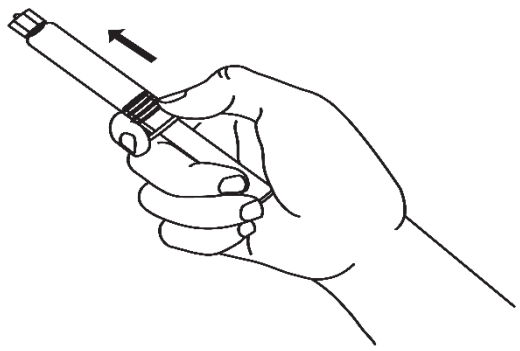
The syringe should only be opened immediately prior to administration.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## Instructions for the use of pre-filled syringe

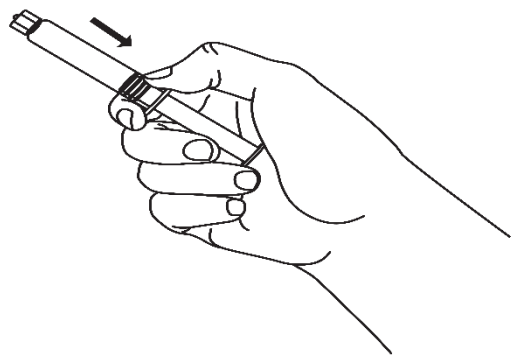
**Step - 1**

| | |
|---|---|
|  | Remove luer cover |

**Step - 2**

| | |
|---|---|
|  | Hold plunger and push barrel forward to relieve any resistance that may be present. |

**Step - 3**

| | |
|---|---|
|  | Pull the barrel down until air is expelled from the syringe. |

**Step - 4**

| | |
|---|---|
| | Attach needle to the luer lock and administer the recommended dose. |

**Step - 5**

| | |
|---|---|
| | Discard any unused portion. |

## 7. MARKETING AUTHORISATION HOLDER

Accord Healthcare B.V.
Winthontlaan 200
3526 KV Utrecht
Nederland

## 8. MARKETING AUTHORISATION NUMBER(S)

RVG 132671

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum eerste verlening van de vergunning: 20 januari 2026

## 10. DATE OF REVISION OF THE TEXT