

Annex III

Summary of Product Characteristics and Package Leaflet

**SUMMARY OF PRODUCT CHARACTERISTICS
AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Aminocaproic acid containing medicinal products>
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aminocaproic acid is indicated for use in patients of all ages in haemorrhage caused by local or general fibrinolysis, including in

Postsurgical haemorrhages in:

- urology (surgery of the bladder and prostate)
- gynaecology (cervical surgery), in patients where tranexamic acid is not available or not tolerated
- obstetrics (post-partum and post-miscarriage haemorrhages) after correction of the coagulation defect
- heart surgery (with or without bypass placement)
- gastroenterology
- odonto-stomatology (dental extractions in haemophiliacs, patients undergoing anticoagulant therapy)

Life-threatening haemorrhages induced by thrombolytics (streptokinase, etc.).

Haemorrhages associated with thrombocytopenia, thrombopenic purpura, leukaemia.

Nonsurgical haematuria of the lower urinary tract (secondary to cystitis, etc.).

Intense menstruations, menorrhagia and haemorrhagic metropathies.

Angioneurotic oedema

4.2. Posology and method of administration

Posology

[If applicable]

<Aminocaproic acid-containing medicinal products> can be administered either orally or intravenously.>

Adults

Intravenous route: The desired blood level is reached with an initial dose of 4 to 5 g by slow intravenous infusion (over one hour), followed by a continuous infusion of 1 g/hour. If treatment needs to be extended, the maximum dose over 24 hours should not normally exceed 24 g.

[If applicable]

<[Oral route: Aminocaproic acid may be given by mouth in an initial dose of 4 to 5 g, followed by 1 to 1.25 g every hour. If treatment needs to be extended, the maximum dose over 24 hours should not normally exceed 24g.]>

Paediatric population

The safety and efficacy of EACA in children aged 0 to 17 years have not been established. However, the following doses have been used in patients aged less than 18 years:

Intravenous route: 100 mg/kg or 3 g/m² by slow intravenous infusion during the first hour, followed by continuous infusion at the rate of 33.3 mg/kg per hour or 1 g/m² per hour. Total dosage should not exceed 18 g/m² (600 mg/kg) in 24 hours.

[If applicable]

<Oral route: 100 mg/kg or 3 g/m² during the first hour, then 33.3 mg/kg per hour or 1 g/m² per hour (maximum 18 g/m² (600 mg/kg) in 24 hours)>

Elderly patients

Dose reductions are not necessary other than in cases of kidney failure.

Renal impairment

A more moderate dose of aminocaproic acid is indicated in patients with kidney failure, together with closer monitoring.

Method of administration

Intravenous route: <Aminocaproic acid-containing medicinal products> should be administered in slow intravenous injection with glycated serum, glucosaline or dextrose.

[If applicable]

<[In oral administration, the content of the ampoule can be drunk as it is or mixed with a little sugared water, broth, milk, etc.]>

In no case should <Aminocaproic acid-containing medicinal products> be administered intramuscularly, as it is a highly hypertonic solution.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Aminocaproic acid should not be used when there is evidence of an active intravascular clotting process (see section 4.4).

4.4. Special warnings and precautions for use

Thrombogenic effect

Numerous clinical studies show that aminocaproic acid has no thrombogenic effect. However, it should be administered with precaution in cases in which the existence of thrombosis or embolism is suspected, and in renal failure.

Fibrinolysis inhibition by aminocaproic acid could theoretically result in clotting or thrombosis. However, there is no clear evidence that the administration of aminocaproic acid has been responsible for the few cases described of intravascular clotting after the treatment. Instead, it appears that said intravascular clotting was probably due to a pre-existing clinical condition, i.e. the presence of DIC. It has been suggested that extravascular clots formed in vivo may not undergo spontaneous lysis like normal clots.

Establishing cause of haemorrhage

When there are doubts regarding whether the aetiology of the haemorrhage which [Invented name] is being used to manage is primary fibrinolysis or disseminated intravascular clotting (DIC), this should be clarified before administering aminocaproic acid. The following tests can be performed to distinguish between the two disorders:

- Platelet count: it is usually reduced in DIC but not in primary fibrinolysis.
- Protamine paracoagulation test: positive in DIC; a precipitate forms when a drop of protamine sulphate is added to "citrate" plasma. This test is negative in primary fibrinolysis.
- Euglobulin clot test: abnormal in primary fibrinolysis and normal in DIC.
- Aminocaproic acid should not be used in DIC without the concomitant administration of heparin.

Haemorrhage of the upper urinary tract

In patients with haemorrhage in the upper urinary tract, the administration of aminocaproic acid has produced intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis or ureters. Aminocaproic acid should therefore not be administered in case of haematuria originating in the upper urinary tract unless the expected benefits more than exceed the risks.

Skeletal muscle effects

On rare occasions, skeletal muscle weakness with muscular fibre necrosis has been described after prolonged administration. Clinical presentation can range from mild myalgia with weakness and fatigue to severe proximal myopathy with rhabdomyolysis, myoglobinuria and acute renal failure. Muscle enzymes, especially creatine phosphokinase (CPK), are elevated. CPK must be monitored in patients undergoing prolonged treatment. The administration of aminocaproic acid should be discontinued if an increase in CPK is observed. The condition remits after administration is suspended; however, the syndrome may recur if the administration of aminocaproic acid is resumed.

When skeletal myopathy occurs, the possibility of damage to the cardiac muscle must also be considered. One case of heart and liver damage has been described in humans. The patient received 2 g of aminocaproic acid every 6 hours to make a total dose of 26 g. The patient died from prolonged cerebrovascular haemorrhage. Necrotic alterations to the heart and liver were found in the post-mortem examination.

Inhibition of plasmin activity

Aminocaproic acid inhibits the effect of plasminogen activators and, to a lesser extent, plasmin activity. This drug must not be administered without a definitive diagnosis and/or laboratory findings indicating hyperfibrinolysis (hyperplasminaemia).

Rapid infusion

Rapid intravenous administration should be avoided, as it can cause hypotension, bradycardia and/or arrhythmias.

Neurological effects

The literature contains publications about an increased incidence of certain neurological deficits such as hydrocephaly, cerebral ischaemia or cerebral vasospasm associated to the use of antifibrinolytic agents in the treatment of subarachnoid haemorrhage (SAH). All these events have also been described as part of the natural evolution of SAH, as a result of diagnostic procedures such as angiography.

Thrombophlebitis

Thrombophlebitis, a possibility with all intravenous treatments, should be avoided, paying special attention to appropriate needle insertion and fixation.

Administration with Factor IX complex concentrate or anti-inhibitor clotting concentrates

Aminocaproic acid should not be administered with Factor IX complex concentrate or anti-inhibitor clotting concentrates, as it could increase the risk of thrombosis.

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

The concomitant administration of clotting factors (Factor IX) and oestrogens can increase the risk of thrombosis.

Laboratory tests: the administration of aminocaproic acid can alter the results of platelet function tests.

4.6. Fertility, pregnancy and breast feeding

Pregnancy

There are no or limited amount of data from the use of epsilon aminocaproic acid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Aminocaproic acid is not recommended during pregnancy.

Women of childbearing potential

Aminocaproic acid is not recommended in women of childbearing potential not using contraception.

Breastfeeding

It is unknown whether epsilon aminocaproic acid is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aminocaproic acid therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of [invented name] on fertility.

The administration of the equivalent to the maximum therapeutic dose in humans in the diet of rats caused fertility disorders in both sexes. The clinical relevance of these findings is unknown (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies have been conducted on the effects on the ability to drive and use machines. In case of dizziness or drowsiness, driving vehicles and using machines is not recommended.

4.8. Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions during treatment are dizziness, hypotension and headache; hypotension is more likely to occur with rapid infusion. Serious cases of myopathy and rhabdomyolysis have been reported; these are generally reversible of discontinuation of treatment but CPK must be monitored in patients undergoing prolonged treatment and treatment stopped if any elevation in CPK occurs.

b. Tabulated list of adverse reactions

The following adverse reactions have been reported from clinical trials, post-authorisation safety studies and from spontaneously-reported cases with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). 'not known' :

System organ class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Very rare ($< 1/10,000$)	Not known*
<i>Blood and lymphatic system disorders</i>		Agranulocytosis, clotting disorders			Leukopenia, thrombocytopenia
<i>Immune system disorders</i>		Allergic and anaphylactoid reactions, anaphylaxis			Maculopapular erythema
<i>Nervous system disorders</i>	Dizziness			Confusion, seizures, delirium, hallucinations, intracranial hypertension, stroke, syncope	
<i>Eye disorders</i>			Reduced vision, watery eyes		
<i>Ear and labyrinth disorders</i>	Tinnitus				
<i>Cardiac disorders</i>	Hypotension	Bradycardia	Peripheral ischaemia		Thrombosis

<i>Respiratory, thoracic and mediastinal disorders</i>	Nasal congestion	Dyspnoea	Pulmonary embolism		
<i>Gastrointestinal disorders</i>	Abdominal pain, diarrhoea, nausea, vomiting				
<i>Skin and subcutaneous tissue disorders</i>		Pruritus, rash			
<i>Musculoskeletal and connective tissue disorders</i>		Muscle weakness, myalgia	Elevated CPK, myositis		Acute myopathy, rhabdomyolysis
<i>Renal and urinary disorders</i>					Renal failure, BUN increased, Nephritic colics and kidney function disorders
<i>Reproductive system and breast disorders</i>					Dry ejaculation
<i>General disorders and administration site conditions</i>	Headache, malaise; injection site reactions, pain and necrosis	Oedema			

* frequency not known (cannot be estimated from the available data).

4.9. Overdose

Aminocaproic acid is not very toxic, so intoxication can only occur in very exceptional cases, such as in cases of relative overdose with kidney failure. In this case, the medicinal product should be adjusted to the degree of kidney failure, or eventually be discontinued.

Some cases of acute overdose have been described after the intravenous administration of aminocaproic acid. The consequences ranged from absence of effects and transient hypotension to acute renal failure resulting in death. One patient with a history of brain tumour and seizures presented seizures after receiving a bolus injection of 8 g of aminocaproic acid. The single dose of aminocaproic acid that produces overdose symptoms or considered to be life threatening is unknown. Some patients have tolerated doses of up to 100 g, while cases of acute kidney failure have been described after a dose of 12 g.

No treatment is known for overdose, although there is evidence that aminocaproic acid is eliminated by haemodialysis and can be eliminated by peritoneal dialysis. The pharmacokinetic studies show that total body clearance of aminocaproic acid is highly diminished in patients with acute kidney failure.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Therapeutic subgroup: Antihemorrhagics
Pharmacotherapeutic group: Antifibrinolytics
ATC code: B02AA01.

Aminocaproic acid is an amino acid that is structurally similar to other physiological amino acids, especially two fundamental amino acids, lysine and arginine. Most of its effects are probably due to this structural similarity.

Aminocaproic acid has multiple pharmacological effects. The most important affect the fibrinolytic enzyme system, the mechanism responsible for dissolving fibrin meshes and, therefore, clots. Aminocaproic acid has an inhibitor effect on this system, which takes place on two levels: on the one hand, at relatively low concentrations, it inhibits the action of plasminogen activators by a competitive mechanism; on the other, at higher concentrations it inhibits plasmin activity. Although the two effects actually have the same results, the first is the most important.

As a result of these effects, aminocaproic acid prevents clot destruction by plasmin and thus prevents the appearance of haemorrhages due to excessive fibrinolytic system activity. However, the anti-haemorrhagic effect of aminocaproic acid is not necessarily linked to the presence of fibrinolysis in blood shown by the respective tests. In fact, the appearance or persistence of a haemorrhage could be, and in many cases is, due to local hyperfibrinolysis, especially when the haemorrhage is in organs rich in plasminogen activators, such as the uterus, prostate, lung, urinary tract, etc. On the other hand, aminocaproic acid has been shown to have a beneficial effect on general haemorrhages, such as those of a haematological origin, in which no hyperfibrinolysis is found in circulating blood.

Plasmin can act on other clotting system components such as factors V and VIII and, in particular, fibrinogen. It has been shown that there are evident relationships between the proteolytic activity of plasmin and the system that forms quinines, polypeptides with different biological effects basically related to inflammation and allergy.

5.2. Pharmacokinetic properties

Aminocaproic acid is rapidly absorbed when administered orally and its peak plasma concentrations are reached after two hours. It is widely distributed (it easily spreads to the tissues, appearing in semen, synovial fluid and foetal tissue) and it is excreted in urine, largely unaltered, with a terminal elimination half life of approximately 2 hours.

5.3. Preclinical safety data

The intravenous and oral lethal dose 50 of aminocaproic acid was 3 and 12 g/kg, respectively, in mice and 3.2 and 16.4 g/kg, respectively, in rats. An intravenous dose of 2.3 g/kg was fatal in dogs. After intravenous administration, tonic-clonic seizures were observed in dogs and mice.

Aminocaproic acid has been observed to give rise to teratogenic effects in rats.

Carcinogenesis, mutagenesis and fertility disorders: No long-term studies have been conducted in animals to evaluate the carcinogenic or mutagenic potential of aminocaproic acid. The administration of the equivalent to the maximum therapeutic dose in humans in the diet of rats caused fertility disorders in both sexes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[Invented name] should not be used with levulose solutions, solutions containing penicillin or with blood.

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal <and other handling>

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the patient

<Aminocaproic acid containing medicinal products>

[See Annex I - To be completed nationally]

Please read all of this leaflet carefully before you start using this medicine.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What <Aminocaproic acid-containing medicinal product> is and what it is used for
2. What you need to know before you take <Aminocaproic acid-containing medicinal products>
3. How to take <Aminocaproic acid-containing medicinal products>
4. Possible side effects
5. How to store <Aminocaproic acid-containing medicinal products>
6. Contents of the pack and other information

1. WHAT Aminocaproic acid containing medicinal product IS AND WHAT IT IS USED FOR

<Aminocaproic acid-containing medicinal products> belongs to a group of medicines called anti-fibrinolytics, i.e. drugs to prevent blood loss (haemorrhage). <Aminocaproic acid-containing medicinal products> is used to prevent blood loss due to excessive bleeding in patients of all ages.

<Aminocaproic acid-containing medicinal products>

[If applicable] < can be administered [either orally or] intravenously, and>

is indicated for the treatment and prevention of blood loss due to excessive bleeding in the following cases:

- postsurgical haemorrhages in urology (bladder and prostate surgery), gynaecology (surgery of the cervix), obstetrics (post-partum and post-abortion haemorrhage), cardiac surgery, gastroenterology, and odontostomatology (dental extractions in haemophiliacs and patients who are receiving anticoagulant therapy);
- significant bleeding induced by thrombolytic drugs;
- bleeding associated with thrombocytopenia (low platelets), thrombocytopenic purpura (bleeding disorder that affects the small vessels) or leukaemia;
- bleeding from the lower urinary tract not caused by surgery (e.g. due to inflammation of the bladder);
- heavy menstrual periods;
- angioneurotic oedema (rapid swelling of the skin, mucosa and submucosal tissues).

2. BEFORE YOU USE <Aminocaproic acid-containing medicinal products>

Do not use <Aminocaproic acid-containing medicinal products>

- If you are allergic to aminocaproic acid or to any of the other ingredients of this medicine.
- If bleeding is due to a condition called disseminated intravascular coagulation.

If you have any further questions, ask your doctor.

Warnings and precautions .

- Talk to your doctor before you are given X:If you have poor kidney function.
- If you have haematuria (blood in urine) from the upper urinary tract.
- If you are prone to the formation of thrombi (blood clots).
- If you need long-term treatment, since muscle alterations may appear.

If you have any further questions, ask your doctor.

Other medicines and X

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicine, even those obtained without a prescription, homeopathic, herbal and other health-related products, as it may be necessary to stop the treatment or adjust the dose of one of them.

Please note that these instructions may also apply to medication that you have used before or you can use later. The administration of <Aminocaproic acid-containing medicinal products> with the following medicines is not recommended:

- Hormonal medication such as oestrogens
- Coagulation factors (Factor IX)

If you have any further questions, ask your doctor or pharmacist.

Pregnancy and breastfeeding

<Aminocaproic acid-containing medicinal products> is not recommended during pregnancy..

If you are pregnant, thinking about becoming pregnant or are breastfeeding, ask your doctor or pharmacist before starting this treatment.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Be aware that you may experience dizziness or disturbed vision during treatment and should not drive or operate machines if affected.

3. HOW TO USE <Aminocaproic acid-containing medicinal products>

Always take <Aminocaproic acid-containing medicinal products> exactly as your doctor has told you.

If in doubt, see your doctor or pharmacist.

Adults:

For intravenous administration: an initial dose of 4 to 5 g will be administered by slow intravenous infusion (one hour) followed by a continuous infusion of 1 g per hour. The maximum daily dose should not exceed 24 g.

[If applicable:]

<For oral administration: an initial dose of 4 to 5 g will be administered, followed by 1 to 1.25 g per hour. If treatment needs to be extended, the maximum dose over 24 hours should not normally exceed 24g.

In oral administration, the contents of the vial can be taken directly or mixed with a little sugar water, broth, milk, etc.

<Aminocaproic acid-containing medicinal products> should not be administered intramuscularly.

Children (0-17 years):

For intravenous administration: 100 mg/kg or 3 g/m² by slow intravenous infusion during the first hour, followed by continuous infusion at the rate of 33.3 mg/kg per hour or 1 g/m² per hour. Total dosage should not exceed 18 g/m² (600 mg/kg) in 24 hours.

[If applicable:]

<For oral administration: 100 mg/kg or 3 g/m² during the first hour, then 33.3 mg/kg per hour or 1 g/m² per hour (maximum 18 g/m² (600 mg/kg) in 24 hours)>

Elderly patients and patients with renal failure:

An adjustment of the dose in patients with impaired renal function should be made. There is no need for dose adjustment in elderly patients.

If you use more <Aminocaproic acid-containing medicinal products> than you should

If you take more <Aminocaproic acid-containing medicinal products> than you should, you may experience a sudden decrease in blood pressure (hypotension), with symptoms including dizziness, fainting, lightheadedness, blurred vision, a rapid, or irregular heartbeat (palpitations), confusion, feeling like you are going to be sick (nausea) or general weakness.

In case of overdose with <Aminocaproic acid-containing medicinal products>, tell your doctor or pharmacist immediately, go to the nearest hospital. Take this leaflet with you.

If you forget to use <Aminocaproic acid-containing medicinal products>

Do not use a double dose to make up for a forgotten dose but continue to use the vials as usual.

4. POSSIBLE SIDE EFFECTS

Like all medicines, aminocaproic acid can cause side effects, although not everybody gets them.

Allergic reactions may occur uncommonly in patients receiving [Invented name] (in fewer than 1 in 100 patients but more than 1 in 1000 patients). The symptoms of a severe allergic reaction may include:

- sudden wheeziness
- chest pain or chest tightness
- swelling of your eyelids, face, lips and tongue
- a lumpy skin rash or 'hives' anywhere on your body
- or a collapse.

You may also uncommonly experience a decrease in white blood cells, which can increase the risk of infection. Symptoms may include severe sore throat with high fever.

If any of these occur during administration of [Invented name] your doctor/surgeon will stop treatment with the drug. If any of these occur while you are taking [Invented name] by mouth, then stop taking [Invented name] and seek immediate medical advice.

Tell your doctor and stop using [invented name] if you experience:

- sudden shortness of breath or difficulty in breathing, sudden coughing for no apparent reason, chest pain and pain on breathing (as these may suggest a blood clot in the lungs),
- unusual aches or pains in your muscles that go on for longer than you might expect (as these can result in kidney problems and potentially life-threatening muscle damage [rhabdomyolysis])

Other side effects are:

Common (affects between 1 and 10 in 100 patients):

- decrease in blood pressure;
- dizziness, ringing or buzzing in ears,
- nasal congestion
- abdominal pain
- diarrhoea
- nausea,
- vomiting
- headache
- discomfort
- pain or skin death at the injection site

Uncommon (affects between 1 and 100 in 1,000 patients):

- problems with bleeding or clotting,
- slow heart beat,
- difficult or laboured breathing,
- itching of the skin,
- rash,
- muscle weakness, pain or aching
- oedema (swelling),

Rare (affects between 1 and 10 in 10,000 patients):

- pain in the arms, legs or lower back, especially pain in the calves or heels upon exertion,

- decreased vision, watery eyes,
- muscular inflammation.

Very rare (affects less than 1 in 10,000 patients):

- confusion
- convulsions
- delirium
- hallucinations
- increased pressure in the brain that can result in severe headache, visual disturbance, vomiting, dizziness, pins and needles, loss of concentration
- stroke
- fainting.

Unknown frequency:

- reduction in blood platelets which increases risk of bleeding or bruising
- kidney failure
- dark-coloured urine, decreased amount or frequency of urine
- skin rash with small, flat, red spots;
- dry ejaculation.

If any of the side effects is serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store <Aminocaproic acid containing medicinal product>

[To be completed nationally]

6. Contents of the pack and other information

What <Aminocaproic acid containing medicinal product> contains

[To be completed nationally]

What <Aminocaproic acid containing medicinal product> looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

[See Annex I - To be completed nationally]

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

[To be completed nationally]