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

Tranexamic 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

Prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year.
Specific indications include:
- Haemorrhage caused by general or local fibrinolysis such as:
  - Menorrhagia and metrorrhagia,
  - Gastrointestinal bleeding,
  - Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract,
- Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions),
- Gynaecological surgery or disorders of obstetric origin,
- Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery,
- Management of haemorrhage due to the administration of a fibrinolytic agent.

4.2 Posology and method of administration

Posology

Adults

Unless otherwise prescribed, the following doses are recommended:

1. Standard treatment of local fibrinolysis:
   0.5 g (1 ampule of 5 ml) to 1 g (1 ampule of 10 ml or 2 ampules of 5 ml) tranexamic acid by slow intravenous injection (= 1 ml/minute) two to three times daily
2. Standard treatment of general fibrinolysis:
   1 g (1 ampule of 10 ml or 2 ampules of 5 ml) tranexamic acid by slow intravenous injection (= 1 ml/minute) every 6 to 8 hours, equivalent to 15 mg/kg BW

Renal impairment

In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contra-indicated in patient with severe renal impairment (see section 4.3). For patient with mild to moderate renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Serum creatinine		Dose IV	Administration
µmol/l	mg/10 ml		
120 to 249	1.35 to 2.82	10 mg/kg BW	Every 12 hours
250 to 500	2.82 to 5.65	10 mg/kg BW	Every 24 hours
> 500	> 5.65	5 mg/kg BW	Every 24 hours

Hepatic impairment

No dose adjustment is required in patient with hepatic impairment.

Paediatric Population:
In children from 1 year, for current approved indications as described in section 4.1, the dosage is in the region of 20 mg/kg/day. However, data on efficacy, posology and safety for these indications are limited.
The efficacy, posology and safety of tranexamic acid in children undergoing cardiac surgery have not been fully established. Currently available data are limited and are described in section 5.1.

Elderly:
No reduction in dosage is necessary unless there is evidence of renal failure.

Method of administration
The administration is strictly limited to slow intravenous injection.

4.3 Contraindications
Hypersensitivity to the active substance or to any of its excipients listed in section 6.1.
Acute venous or arterial thrombosis (see section 4.4 Special)
Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding (see section 4.4)
Severe renal impairment (risk of accumulation)
History of convulsions
Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)

4.4 Special warnings and precautions for use
The indications and method of administration indicated above should be followed strictly:
• Intravenous injections should be given very slowly
• Tranexamic acid should not be administered by the intramuscular route.

Convulsions
Cases of convulsions have been reported in association with tranexamic acid treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following intravenous (i.v.) injection of tranexamic acid in high doses. With the use of the recommended lower doses of TXA, the incidence of post-operative seizures was the same as that in untreated patients.

Visual disturbances
Attention should be paid to possible visual disturbances including visual impairment, vision blurred, impaired colour vision and if necessary the treatment should be discontinued. With continuous long-term use of TXA solution for injection, regular ophthalmologic examinations (eye examinations including visual acuity, colour vision, fundus, visual field etc.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, the physician must decide after consulting a specialist on the necessity for the long-term use of TXA solution for injection in each individual case.

Haematuria
In case of haematuria from the upper urinary tract, there is a risk for urethral obstruction.

Thromboembolic events
Before use of TXA, risk factors of thromboembolic disease should be considered. In patients with a history of thromboembolic diseases or in those with increased incidence of thromboembolic events in their family history (patients with a high risk of thrombophilia), Tranexamic acid solution for injection should only be administered if there is a strong medical indication after consulting a physician experienced in hemostaseology and under strict medical supervision (see section 4.3).
Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (See section 4.5.).

Disseminated intravascular coagulation
Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid (see section 4.3). If tranexamic acid is given it must be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding. Characteristically, the haematological profile approximates to the following: reduced euglobulin clot lysis time; prolonged prothrombin time; reduced plasma levels of fibrinogen, factors V and VIII, plasminogen fibrinolysin and alpha-2 macroglobulin; normal plasma levels of P and P complex; i.e. factors II (prothrombin), VIII and X; increased plasma levels of fibrinogen degradation products; a normal platelet count. The foregoing presumes that the underlying disease state does not of itself

modify the various elements in this profile. In such acute cases a single dose of 1g tranexamic acid is frequently sufficient to control bleeding.. Administration of Tranexamic acid in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field. Medicinal products that act on haemostasis should be given with caution to patients treated with tranexamic acid. There is a theoretical risk of increased thrombus-formation potential, such as with oestrogens. Alternatively, the antifibrinolytic action of the drug may be antagonised with thrombolytic drugs.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy:
There is insufficient clinical data on the use of tranexamic acid in pregnant women. As a result, although studies in animals do not indicate teratogenic effects, as precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy. Limited clinical of the use of tranexamic acid in different clinical haemorrhagic settings during the second and third trimesters did not identify deleterious effect for the foetus. Tranexamic acid should be used throughout pregnancy only if the expected benefit justifies the potential risk.

Breastfeeding:
Tranexamic acid is excreted in human milk. Therefore, breastfeeding is not recommended.

Fertility:
There are no clinical data on the effects of Tranexamic acid on fertility.

4.7 Effects on ability to drive and use machines

No studies have been performed on the ability to drive and use machines.

4.8 Undesirable effects

The ADRs reported from clinical studies and post-marketing experience are listed below according to system organ class.

Tabulated list of adverse reactions
Adverse reactions reported are presented in table below. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), not know (can not be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Skin and subcutaneous tissue disorders	Uncommon	- Dermatitis allergic
Gastrointestinal disorders	Common	- Diarrhoea - Vomiting - Nausea
Nervous system disorders	Not known	- Convulsions particularly in case of misuse (refer to sections 4.3 and 4.4)
Eye disorders	Not known	- Visual disturbances including impaired colour vision

Vascular disorders	Not known	- Malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration) - Arterial or venous thrombosis at any sites
Immune system disorders	Not known	- Hypersensitivity reactions including anaphylaxis

4.9 Overdose

No case of overdose has been reported.
Signs and symptoms may include dizziness, headache, hypotension, and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose.
Management of overdose should be supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, Antifibrinolytics
ATC code: B02AA02
Tranexamic acid exerts an anti haemorrhagic activity by inhibiting the fibrinolytic properties of plasmin.
A complex involving tranexamic acid, plasminogen is constituted; the tranexamic acid being linked to plasminogen when transformed into plasmin.
The activity of the tranexamic acid-plasmin complex on the activity on fibrin is lower than the activity of free plasmin alone.
In vitro studies showed that high tranexamic dosages decreased the activity of complement.

Paediatric population
In children over one year old:
Literature review identified 12 efficacy studies in paediatric cardiac surgery which have included 1073 children, 631 having received tranexamic acid. Most of them were controlled versus placebo. Studied population was heterogenic in terms of age, surgery types, dosing schedules. Study results with tranexamic acid suggest reduced blood loss and reduced blood product requirements in paediatric cardiac surgery under cardiopulmonary bypass (CPB) where there is a high risk of haemorrhage, especially in cyanotic patients or patients undergoing repeat surgery. The most adapted dosing schedule appeared to be:
- first bolus of 10 mg/kg after induction of anaesthesia and prior to skin incision,
- continuous infusion of 10 mg/kg/h or injection into the CPB pump prime at a dose adapted on the CPB procedure, either according to a patient weight with a dose of 10 mg/kg dose, either according to CPB pump prime volume, last injection of 10 mg/kg at the end of CPB.

While studied in very few patients, the limited data suggest that continuous infusion is preferable, since it would maintain therapeutic plasma concentration throughout surgery.
No specific dose-effect study or PK study has been conducted in children.

5.2 Pharmacokinetic properties

Absorption
Peak plasma concentrations of tranexamic acid are obtained rapidly after a short intravenous infusion after which plasma concentrations decline in a multi-exponential manner.
Distribution
The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. The initial volume of distribution is about 9 to 12 liters.
Tranexamic acid passes through the placenta. Following administration of an intravenous injection of 10 mg/kg to 12 pregnant women, the concentration of tranexamic acid in serum ranged 10-53 µg/mL while that in cord blood ranged 4-31 µg/mL. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. Following administration of an intravenous injection of 10 mg/kg to 17 patients undergoing knee surgery, concentrations in the joint fluids were similar to those seen

in corresponding serum samples. The concentration of tranexamic acid in a number of other tissues is a fraction of that observed in the blood (breast milk, one hundredth; cerebrospinal fluid, one tenth; aqueous humor, one tenth). Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.
Excretion
It is excreted mainly in the urineas unchanged drug. Urinary excretion via glomerular filtration is the main route of elimination. Renal clearance is equal to plasma clearance (110 to 116 mL/min). Excretion of tranexamic acid is about 90% within the first 24 hours after intravenous administration of 10 mg/kg body weight. Elimination half-life of tranexamic acid is approximately 3 hours
Special populations
Plasma concentrations increase in patients with renal failure.
No specific PK study has been conducted in children.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. Epileptogenic activity has been observed in animals with intrathecal use of tranexamic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[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

Package leaflet: Information for the patient

<Tranexamic acid – containing medicinal products>

<[See Annex I - To be completed nationally]>

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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What <Tranexamic acid – containing medicinal products> is and what it is used for

<Tranexamic acid – containing medicinal products> contains tranexamic acid which belongs to a group of medicines called antihaemorragics; antifibrinolitics, aminoacids.
<Tranexamic acid – containing medicinal products> is used in adults and children above one year of age for the prevention and treatment of bleeding due to a process that inhibits blood clotting called fibrinolysis.
Specific indications include:
- Heavy periods in women
- Gastrointestinal bleeding
- Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract
- Ear, nose, or throat surgery
- heart, abdominal, or gynecological surgery
- bleeding after you have been treated with another medicine to break down blood clots.

2. What you need to know before you are given <Tranexamic acid – containing medicinal products>

Do not take <Tranexamic acid – containing medicinal products> if you:
- are allergic to tranexamic acid or any of the other ingredients of this medicine (listed in section 6)
- have currently a disease leading to blood clots
- have a condition called 'consumption coagulopathy' where blood in the whole body starts to clot
- have kidney problems.
- have a history of convulsions.

Due to the risk of cerebral oedema and convulsions, intrathecal and intraventricular injection and intracerebral application are not recommended.

If you think any of these apply to you, or if you are in any doubt at all, tell your doctor before taking <Tranexamic acid – containing medicinal products>.

Warnings and precautions
Tell your doctor if any of these apply to you to help him or her decide if <Tranexamic acid – containing medicinal products> is suitable for you:
- If you have had blood in your urine <Tranexamic acid – containing medicinal products> it may be lead to urinary tract obstruction.
- If you have a risk of having blood clots.

- If you have excessive clotting or bleeding throughout your body (disseminated intravascular coagulation), <Tranexamic acid – containing medicinal products> may not be right for you, except if you have acute severe bleeding and blood test have shown the process that inhibits blood clotting called fibrinolysis is activated.
- If you have had convulsions, <Tranexamic acid – containing medicinal products> should not be administered. Your doctor must use the minimal dose possible to avoid convulsions following treatment with <Tranexamic acid – containing medicinal products>
- If you are on a long-term treatment with X, attention should be paid to possible disturbances of colour vision and if necessary the treatment should be discontinued. With continuous long-term use of <Tranexamic acid-containing medicinal products> solution for injection, regular ophthalmologic examinations (eye examinations including visual acuity, colour vision, fundus, visual field etc.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, your doctor must take a decision after consulting a specialist on the necessity for the long-term use of <Tranexamic acid-containing medicinal products> solution for injection in your case.

Other medicines and <Tranexamic acid – containing medicinal products>
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, vitamins, minerals, herbal medicines or dietary supplements.
You should specifically tell your doctor if you take:
- other medicines that help blood to clot called antifibrinolytic medicines
- medicines that prevent blood clotting, called thrombolytic medicines
- oral contraceptives

Pregnancy and breast-feeding
Ask your doctor for advice if you are pregnant or breast-feeding before taking <Tranexamic acid – containing medicinal products>.
Tranexamic acid is excreted in human milk. Therefore, the use of <Tranexamic acid – containing medicinal products> during breast-feeding is not recommended.

Driving and using machines
No studies have been performed on the ability to drive and use machines.

3. How to take Use in Adults
<Tranexamic acid – containing medicinal products>solution for injection will be given to you by slow injection into a vein.
Your doctor will decide the correct dose for you and how long you should take it.

Use in children
If <Tranexamic acid – containing medicinal products> solution for injection is given to a child from one year, the dose will be based on the child's weight. Your doctor will decide the correct dose for the child and how long he/she should take it.

Use in elderly
No reduction in dosage is necessary unless there is evidence of renal failure.

Use in patients with kidney problem
If you a kidney problem, your dose of tranexamic acid will be reduced according to a test performed on your blood (serum creatinine level).

Use in patients with hepatic impairment
No reduction in dosage is necessary.

Method of administration
<Tranexamic acid – containing medicinal products> should only be administrated slowly into a vein.
<Tranexamic acid – containing medicinal products> must not be injected into a muscle.

If you are given more <Tranexamic acid – containing medicinal products> than the recommended dose

If you are given more <Tranexamic acid – containing medicinal products> than the recommended dose you may experience a transitory blood pressure lowering. Talk to a doctor or pharmacist immediately.

4. Possible side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported with <Tranexamic acid – containing medicinal products> are:

The following side effects have been observed with <Tranexamic acid – containing medicinal products>

Common (may affect up to 1 in 10 users)

- effects on the stomach and intestines: nausea, vomiting, diarrhoea

Uncommon (may affect 1 to 10 in 1000 users)

- effects on the skin problems : rash

Not know (frequency cannot be estimated from the available data)

- malaise with hypotension (low blood pressure), especially if the injection is given too quickly
- blood clots
- effects on the nervous system: convulsions
- effects on the eyes : vision disturbances including impaired color vision
- effects on the immune system : allergic reactions

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

5. How to store <Tranexamic acid – containing medicinal products>

[To be completed nationally]

6. Contents of the pack and other information

What <Tranexamic acid – containing medicinal products> contains

[To be completed nationally]

What <Tranexamic acid – containing medicinal products> looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

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

[To be completed nationally]