The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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CPMP/902/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 10 REFERRAL

CYKLO-f

International Nonproprietary Name (INN): **Tranexamic acid**

BACKGROUND INFORMATION

In March 1999 Pharmacia & Upjohn submitted applications for Mutual Recognition of the Marketing Authorisation granted by the Competent Authority in Sweden, acting as Reference Member State, for Cyklo-f tablets. The Mutual Recognition procedure started on 03 April 1999. The Concerned Member States were Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Spain, and The Netherlands. The Concerned Member State, Germany considered that there were grounds for supposing that the authorisation of Cyklo-f may present a risk to public health and referred the matter to the CPMP under article 10 of Directive 75/319/EEC on 02 July 1999.

The public health risk raised by Germany related to the scientific basis of the dose recommendation, specifically the lack of clinical trials performed according to current standards confirming the recommended dose schedule.

The Marketing Authorisation Holder provided written responses on 6 September 1999 and on 15 December 1999.

Cyklo-f is supplied as white, capsular film coated tablets containing 500 mg of the active substance tranexamic acid, which is an anti-fibrinolytic, haemostatic agent acting by competitive inhibition of the activation of plasminogen to plasmin. This inhibition results in a stabilisation of formed fibrin which otherwise would have become lysed by plasmin.

Tranexamic acid has been marketed in many EU countries under the tradename Cyklokapron for more than three decades for the treatment of haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis (including thrombolytic overdose) and for the treatment of menorrhagia. Cyklokapron tablets contain 500 mg tranexamic acid. The recommended dose of Cyklokapron for menorrhagia in the different European countries is 2-3 tablets 2-4 times daily for 3-4 days.

In order to support the CPMP evaluation of the matter of arbitration data from 6 clinical trials and postmarketing experience were submitted. The data indicated that 3 g tranexamic acid per day is the lowest clinically significant effective daily dose and that higher doses reduce the menstrual blood loss to a greater degree. The risk for experiencing gastrointestinal adverse events - although of mild nature - is increased at 6 g per day. Three days treatment would appear to be sufficient for most women, but for some it may be advantageous to extend the treatment to 4 days. Therefore, it seems justifiable to recommend 3 g per day as the normal dosage and, if needed, an increase to 4 g per day for 3-4 days.

Although most of the studies reviewed have not been performed according to current standards, the concordance in results justifies their use for the dose recommendation. Furthermore, the overall data accumulated over a period of more than three decades extensive human exposure to tranexamic acid do not indicate that Cyklo-f in the proposed indication and dose range would raise any major safety or efficacy

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concerns. Therefore, although the submitted documentation is not according to the current standards, it supports a positive overall benefit/risk of Cyklo-f for menorrhagia at the recommended dose schedule.

The CPMP having considered the written responses provided by the Applicant, the Rapporteur/Co-Rapporteur's assessment reports and the comments from CPMP members was of the opinion that the public health risk issue raised by Germany should not prevent the granting of a marketing authorisation.

The CPMP adopted a positive opinion on 20 January 2000 recommending the granting of the Marketing Authorisation for Cyklo-f with amendments to the Summary of Product Characteristics (SPC) of the Reference Member State.

During the Standing Committee phase, the "Agence Francaise de Sécurite Sanitaire des Produits de Santé" informed the European Commission about a potential risk to public health with regard to the information in section 4.8 "Undesirable effects" of the SPC. This section included information on side-effects at 6 g daily dose, which is higher than the recommended 4 g maximum daily dose (as mentioned in section 4.2 "Posology and method of administration"). This information could be inadequately interpreted by prescribers who could consider 6 g as the maximum daily dose authorised instead of 4 g.

In a letter dated 14 April 2000, the Commission informed the EMEA that on the basis of the concern raised by France the Decision making process had been suspended and that the application was referred back to the EMEA for further consideration.

The CPMP agreed with the French Agency that the wording concerning the dose of 6 g as the maximum daily dose could be inadequately interpreted by the prescribing physicians, particularly with regard to the authorised maximum daily dose of 4 g. Therefore, the reference to side-effects at 6 g was deleted.

Since the positive risk/benefit ratio of Cyklo-f for the claimed indication and posology was maintained, the CPMP adopted a revised positive opinion on 25 May 2000 recommending the granting of the Marketing Authorisation for Cyklo-f with amendments to the SPC of the Reference Member State.

An overall summary of the scientific evaluation is provided, together the the amended SPC.

On the basis of the Opinion adopted by the CPMP the European Commission issued a Decision on 27 July 2000.

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CYKLO-F

Tranexamic acid has been marketed in many EU countries under the tradename Cyklokapron for more than three decades for the treatment of haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis (including thrombolytic overdose) and for the treatment of menorrhagia. Cyklo-f tablets 500 mg are identical to Cyklokapron tablets 500 mg, the only differences being the restricted indication to menorrhagia and the pack size.

The main issue for arbitration was the scientific justification for the dose recommendation. Further issues addressed in the course of the evaluation were the validity of the pharmakokinetic/pharmacodynamic and the clinical efficacy data to support the efficacy in the proposed indication. It was concluded that the documentation would be considered insufficient for a new medicinal product, because the available studies are not in accordance with the current requirements. However, the totality of the data accumulated over a period of more than three decades is comprehensive and provides adequate evidence for the efficacy and safety of tranexamic acid in the treatment of menorrhagia. Regarding the main issue of arbitration, i.e. the scientific justification of the recommended dose, it was concluded that the available studies suggest that the recommended dose of 2 tablets 3 times daily for 3-4 days (and a maximun daily dose of 4 g) induces a clinically relevant reduction in menstrual blood by approximately 40 % without inducing significant adverse events. Increase of the daily dose to 6 g results in a dose-dependent increase in efficacy, albeit concomitantly with an increase of mild gastrointestinal adverse events. Hence, the submitted documentation, although not according to the current standards, supports the recommended dose.

In summary, it was concluded that when assessing the risk/benefit of Cyklo-f the deficiencies in the product documentation have to be viewed against the current “state of the art” conception of tranexamic acid. Based on the extensive clinical experience accumulated for more than three decades and the submitted documentation the overall benefit-risk of Cyklo-f in the treatment of menorrhagia can be considered as positive.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- In order to protect the patient from taking an unnecessary number of tablets if menorhagia is limited to less than four days, the duration of the dosing should be amended from “for 3-4 days” to ”as long as needed for up to 4 days”;
- Cyklo-f is contraindicated in patients with severe renal failure (see 4.3.) the dose recommendation for serum creatinine >500 μmol/l has been deleted and the phrase dose recommendation “for patients with impaired renal function” should be amended to dose recommendation “for patients with mild to moderate renal insufficiency;
- Tranexamic acid should not be strictly contraindicated in rare cases of very strong bleeding due to increased fibrinolysis due to disseminated intravascular coagulation, this contraindication should be deleted and replaced by a special warning: **“**The use of tranexamic acid in cases of increased fibrinolysis due to disseminated intravascular coagulation is not recommended”;
- The available i.v. data were considered sufficient to define a dose recommendation in renal insufficiency, the related wording in the section “Special warnings and precaution for use” should be amended accordingly;
- The pharmacodynamic properties should be clarified to focus on the role of tranexamic acid as symptomatic treatment for menorrhagia;
- Relevant preclinical information is missing, appropriate data should be included;

- The mention of the occurrence of an undesirable effect at a higher dose than recommended in the section “Undesirable effects” is not appropriate;

the CPMP has recommended the amendment of the Summary of Product Characteristics as set out in Annex III of the Opinion.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cyklo-f 500 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains tranexamic acid 500 mg
Other ingredients, refer to 6.1

3. PHARMACEUTICAL FORM

White, capsular, film coated tablets engraved with a score and with arcs above and below the letters CY.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Menorrhagia

4.2. Posology and method of administration

Recommended dosage is 2 tablets 3 times daily as long as needed for up to 4 days. If very heavy menstrual bleeding, dosage may be increased. A total dose of 4 g daily (8 tablets) should not be exceeded. Treatment with Cyklo-f should not be initiated until menstrual bleeding has started.

By extrapolation from clearance data relating to the intravenous dosage form, the following reduction in the oral dosage is recommended for patients with mild to moderate renal insufficiency.

Serum creatinine (µmol/l)	Dose tranexamic acid
120-249	15 mg/kg body weight twice daily
250-500	15 mg/kg body weight/day

4.3. Contraindications

Cyklo-f for menorrhagia is contraindicated in women with:

Active thromboembolic disease;
Severe renal failure because of risk of accumulation;
Hypersensitivity to tranexamic acid or any of the ingredients.

4.4. Special warnings and special precautions for use

Patients with irregular menstrual bleeding should not use Cyklo-f until the cause of irregular bleeding has been established.
If menstrual bleeding is not adequately reduced by Cyklo-f, an alternative treatment should be considered.

Patients with a previous thromboembolic event and a family history of thromboembolic disease (patients with thrombophilia) should use Cyklo-f only if there is a strong medical indication and under strict medical supervision.

The blood levels are increased in patients with renal insufficiency. Therefore a dose reduction is recommended (see 4.2).

The use of tranexamic acid in cases of increased fibrinolysis due to disseminated intravascular coagulation is not recommended.

In haematuria from the upper urinary tract clot formation can, in a few cases, lead to ureteric obstruction.

Clinical experience with Cyklo-f in menorrhagic children under 15 years of age is not available.

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

Clinically important interactions have not been observed with tranexamic acid tablets. Due to the absence of interaction studies, simultaneous treatment with anticoagulants must be under the strict supervision of a physician experienced in this field.

4.6. Pregnancy and lactation

Cyklo-f is intended for treatment of menorrhagia only; it should not be used during pregnancy.

Pregnancy: Tranexamic acid crosses the placenta. Clinical experience of use in pregnant women is limited. Animal studies have not shown any evidence of an increased incidence of foetal damage.

Lactation: Tranexamic acid is excreted into breast milk, but is not likely to influence the child at therapeutic doses.

4.7. Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8. Undesirable effects

Dose-dependent gastrointestinal discomfort is the most commonly reported undesirable effect, but it is usually of mild and temporary nature. Allergic skin reactions have been reported as an uncommon undesirable effect.

Frequency of undesirable effects at a dose of 4 g/day

Common (>1/100)	*GI:* Nausea, vomiting, diarrhoea
Less common (< 1/100)	*Skin:* Allergic skin reactions

Adverse Events:
Rare cases of adverse events have been reported with use of tranexamic acid; thromboembolic events, impaired colour vision and other visual disturbances and dizziness.

4.9. Overdose

Symptoms: Nausea, diarrhoea, dizziness, and headache. Orthostatic symptoms, hypotension and myopathy may occur. Risk of thrombosis in predisposed individuals.

Treatment of overdose: Initiate vomiting, then gastric lavage, charcoal therapy and symptomatic treatment. Maintain adequate diuresis. Anticoagulant treatment should be considered.

Toxicity: 37 g of tranexamic acid caused mild intoxication in a seventeen-year-old after gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Cyklo-f contains tranexamic acid, an antifibrinolytic which is an inhibitor of the activation of plasminogen to plasmin in the fibrinolytic system. The treatment of menorrhagia is symptomatic since it does not affect the underlying pathogenesis of the increased menstrual flow.

5.2. Pharmacokinetic properties

The bioavailability is approximately 35 % in the dose range of 0.5 – 2 g and it not affected by simultaneous food intake. Following a single oral dose, C_{max} and urinary excretion increased linearly with doses between 0.5 g and 2 g. Following a single oral dose of 0.5 g, C_{max} is approx. 5 µg/ml and after a dose of 2 g C_{max} is 15 µg/ml.
Therapeutic concentration is maintained in plasma up to 6 hours after an oral single dose of 2 g. Binding to plasma proteins (plasminogen) is approximately 3% at therapeutic plasma levels. Plasma clearance is approximately 7 l/hour. Prevailing plasma half-life is approximately 2 hours following a single intravenous dose. After repeated oral administration the half-life is longer. The terminal half-life is about 3 hours. Approximately 95% of the absorbed dose is excreted unchanged in the urine. Two metabolites have been identified: an N-acetylated and a deaminated derivative. Impaired kidney function constitutes a risk for accumulation of tranexamic acid.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans in addition to those included in other sections of the SPC. These data have been based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity and carcinogenicity.
Retinal abnomalities were found in long term toxicity studies in dog and cat: increased reflectivity, photoreceptor segment atrophy, peripheral retinal atrophy, atrophy of rods and cones. These ocular changes were dose related and occurred in high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Hydroxypropylcellulose
Talc
Magnesium stearate
Silica, colloidal anhydrous
Povidone

Tablet coating:
Methacrylate polymers
Titanium dioxide (E171)
Talc
Magnesium stearate

Macrogel 8000
Vanillin.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

Carton containing 18 tablets in a blister (PVC/PVDC/Aluminium)

6.6. Instructions for use and handling

None.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT