

**CYKLO-F-500MG FILM-COATED TABLETS
(TRANEXAMIC ACID)**

PL 19477/0018

UK Public Assessment Report

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Viatrix Pharmaceutical Limited (trading as Meda Pharmaceuticals) a Marketing Authorisation (licence) for the medicinal product Cyklo-F-500mg Film Coated Tablets (PL 19477/0018) on 31st March 2010. This is a Pharmacy (P) only supply medicine.

The application was a reclassification application by which the legal status of the product was changed from a prescription only medicine (POM) to pharmacy (P) only supply.

Cyklo-F-500mg Film Coated Tablets contains the active ingredient tranexamic acid, which belongs to a group of medicines called anti-fibrinolytics. These are used to control bleeding. When you bleed your blood forms clots to stop bleeding. In some people these clots break down causing too much bleeding. Cyklo-F- stops these clots from dissolving and so reduces bleeding. It is used to reduce heavy menstrual bleeding over several cycles in women with regular menstrual cycles.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Cyklo-F-500mg Film Coated Tablets outweigh the risk; hence a Marketing Authorisation (MA) has been granted.

**CYKLO-F-500MG FILM-COATED TABLETS
(TRANEXAMIC ACID)**

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Viatris Pharmaceutical Ltd (trading as Meda Pharmaceuticals) a Marketing Authorisation for the medicinal product Cyklo-F-500mg Film Coated Tablets (PL 19477/0018) on 31st March 2010. The product is a Pharmacy (P) only supply indicated for the reduction of heavy menstrual bleeding over several cycles in women with regular cycles.

The application was submitted as a simple abridged application in association with a reclassification application, and cross refers to the approved product, Cyklokapon Tablets (PL 15142/0004), a POM licence currently authorised to MEDA Pharmaceuticals Limited on 27th July 2005, the product has been through a number of change of ownerships but was originally authorised on 22nd December 2004 to Viatris Pharmaceuticals Limited.

The Marketing Authorisation application was assessed in parallel with the reclassification application. The approved Marketing Authorisation (MA) is identical to the reference MA, apart from some differences which relate directly to the reclassification. The reclassification of the product, from POM to P status has been assessed and deemed satisfactory, following review by the Committee on Safety of Medicines (CSM) and Expert Advisory Group on Oncology and Haematology.

No new data was submitted nor was it necessary for this simple application, as the data is identical to that of the previously granted cross-reference product.

Cyklo-F-500mg Film Coated Tablets contains the active ingredient tranexamic acid, which belongs to a group of medicines called anti-fibrinolytics. These are used to control bleeding. Cyklo-F-500mg Film Coated Tablets is used to reduce heavy bleeding during the menstrual cycle.

PHARMACEUTICAL ASSESSMENT

LICENCE NO:	PL 19477/0018
PROPRIETARY NAME:	Cyklo-F-500mg Film Coated Tablets
ACTIVE(S):	Tranexamic Acid
COMPANY NAME:	Viatrix Pharmaceuticals Limited
LEGAL STATUS:	P

1. INTRODUCTION

This is a reclassification application for pharmacy only availability of Cyklo-F-500mg Film Coated Tablets, containing tranexamic acid, to be available for the treatment of reducing heavy menstrual bleeding over several cycles in women, aged 18-45 years, with regular 21-35 day cycles with no more than 3 days individual variability in cycle duration. The proposed name is Cyklo-F-500mg Film-Coated Tablets and the proposed dosage is:

‘Cyklo-f therapy is initiated only once heavy bleeding has started. The recommended dosage is 2 tablets 3 times daily for as long as needed, but for a maximum of 4 days. If there is very heavy menstrual bleeding, the dosage may be increased. A total dose of 4 g daily (8 tablets) should not be exceeded.’

The reclassification application is linked to a simple abridged application. The Marketing Authorisation (MA) cross refers to the approved product, Cykloapron Tablets 500mg Film Coated Tablets (PL 15142/0130), a POM licence currently held by MEDA Pharmaceutical Limited, authorised on 19th August 2009 following a Change of Ownership. This cross reference product is used to prevent or reduce bleeding following prostrate surgery, heavy periods, nose bleeds, cervical surgery, bleeding inside the eye, tooth removal in haemophiliacs and in the treatment of a hereditary disease called angioneurotic oedema.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed product name is Cyklo-F-500mg Film Coated Tablets. The product has been named in line with current requirements and the proposed name is acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Cyklo-F-500mg Film Coated Tablets contains the active ingredient tranexamic acid. The tablets are supplied in blister packs consisting of polyvinylchloride/polyvinylidene chloride (PVC/PVdC) with aluminium foil backing containing 18 tablets.

The proposed shelf-life (3 years) and storage conditions (Do not store above 25°C) are consistent with the details registered for the cross-reference product.

2.3 Legal status

The product is available as a Pharmacy (P) only medicine.

2.4 Marketing Authorisation holder / Contact Persons / Company

The approved Marketing Authorisation holder is:

Viatrix Pharmaceuticals Ltd
Sherwood House
7 Gregory Boulevard
Nottingham
NG7 6LB
UK

Trading as:

Meda Pharmaceuticals
Regus House
Herald Way
Pegasus Business Park
Castle Donington
Derbyshire
DE74 2TZ
UK

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product / shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance

No materials of animal or human origin are included in the product. This is consistent with the cross reference product.

3. EXPERT REPORTS

Satisfactory expert reports and Curriculum Vitae of experts are provided.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the approved product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) and LABELLING

The proposed SmPC, PIL and labelling are consistent with the product agreed for reclassification.

The PIL has been prepared in the user tested format and in line with the SmPC and details agreed for the reclassification of this product. The approved PIL is satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

6.2 Carton and blister

The approved artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application is acceptable. The applicant has complied with all the requirements both for the abridged application and the reclassification.

The applicant has proposed suitable documents for pharmacy training and a questionnaire to ensure safe supply.

The grounds for this application are considered adequate. There are no pharmaceutical issues to address. It is recommended that a Marketing Authorisation is granted.

RECLASSIFICATION ASSESSMENT

1. INTRODUCTION

Meda Pharmaceuticals has submitted a variation application for the legal reclassification from Prescription Only Medicine (POM) to Pharmacy (P) availability of Cyclo-f tablets for the indication of “reduction of heavy menstrual bleeding in women with regular 21-35 day cycles with no more than 3 days individual variability in cycle duration.” The present POM product is indicated for: “Short term use for haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis. Local fibrinolysis as occurs in the following conditions: prostatectomy and bladder surgery, menorrhagia, epistaxis, conisation of the cervix, traumatic hyphaema. Hereditary angioneurotic oedema and management of dental extraction in haemophiliacs.”

2. BACKGROUND

Tranexamic acid is an antifibrinolytic agent that is a competitive inhibitor of the activation of plasminogen to plasmin. Patients with menorrhagia have been found to have increased levels of plasminogen activators in the endometrium compared to those with normal blood loss. Tranexamic acid is not thrombogenic and does not induce a general prothrombotic state. Tranexamic acid, under the trade name Cylcokapron was first licensed in Austria in 1966, and subsequently licensed in the UK in 1972. Cyclo-f was granted non-prescription status in Sweden for the treatment of menorrhagia in 1997, which appears to be the only country, currently, where it is available without prescription. Since then, there have been two unsuccessful reclassification applications in the UK in 1998 and 1999. CSM considered that menorrhagia was not an appropriate indication for self-diagnosis and that the safety profile of tranexamic acid in this indication was uncertain, in particular with regard to thromboembolism.

3. PHARMACEUTICAL COMMENT

This is a variation application and no pharmaceutical changes have been proposed. Pharmaceutical comments on aspects of the reclassification application, such as the product information and pharmacy training, have been included in the relevant sections of the report.

4. MEDICAL ASSESSMENT

4.1 Clinical background and current medical management

The proposed posology is reduction of heavy menstrual bleeding in women with regular (21-35 day) cycles with no more than 3 days individual variability in cycle duration. In the RCOG guidelines on The Initial Management of Menorrhagia (Annex 3) menorrhagia is described as “ A history of heavy cyclical menstrual loss over several consecutive cycles...” Menorrhagia has also been defined as menstrual blood loss exceeding 80 mL per cycle. Approximately 10% of the female population of reproductive age has blood loss exceeding 80mL and 5-15% of women are thought to be affected by blood loss to such a degree that treatment should be considered. The

treatment objective is to alleviate heavy blood loss and consequently improve quality of life and iron deficiency anaemia. In practice menorrhagia is defined by a woman's subjective assessment of blood loss, which has a poor correlation with objective measures. It is considered by the applicant that there is an ongoing change in the view of menorrhagia, from a medically defined disease to a subjectively perceived illness and from a question on iron deficiency to a matter of quality of life. The Royal College of Obstetricians and Gynaecologists (RCOG) guideline recommends that before treatment a history of heavy clinical menstrual blood loss should be obtained, an abdominal and pelvic examination should be performed, and a full blood count should be obtained. The expert report presents the argument that most GPs do not carry out a pelvic examination or full blood count in patients presenting with menorrhagia. In addition, it is sub-mucous fibroids that are assumed to cause menorrhagia, and these can only be detected by ultrasound scan and/or hysteroscopy; therefore the benefit of vaginal examination by GPs is said to be questionable.

The RCOG guideline recommends either mefenamic acid or tranexamic acid as first line therapy starting on the first day of period for days of heavy flow for patients that do not require contraception or prefer non-hormonal treatment. Hormonal treatment, usually in the form of norethisterone is given to those also requiring contraception. All of these medications are available only on prescription. The clinical expert considers that "The present system whereby women must seek a medical opinion before beginning medical treatment for menorrhagia may result in the majority of women receiving the wrong treatment. Data from the Somerset Morbidity Project shows that norethisterone, which is ineffective, still appears to be the most commonly prescribed treatment for menorrhagia (37%). Mefenamic acid, which is effective, but less so than tranexamic acid, is given to 27% of patients. Tranexamic acid, which is the most effective oral medication... is only prescribed to 15% of women."

Assessor's comment:

The proposed indication does not reflect the RCOG definition of menorrhagia. The indication should be amended to "heavy cyclical menstrual bleeding over several consecutive cycles". Menorrhagia is a symptom that may also be associated with a number of disorders, which include local pathology (endometriosis, polyps, submucosal fibroids, endometrial hyperplasia, and endometrial carcinoma), general disorders (hypothyroidism), haematological disorder (Van Willebrands), and iatrogenic cause (IUD). In the majority of cases of menorrhagia no underlying pathology is found. The proposed clinical management of menorrhagia is not in line with the current RCOG guideline on The Initial Management of Menorrhagia. The question is whether bypassing the initial assessment and referral process recommended by the guideline represents an acceptable risk (See also section 6.1 of this report). The applicant considers that currently the majority of women receive a less effective treatment for menorrhagia than tranexamic acid. The efficacy of a medication relative to other options also available on prescription should not be a factor in determining the legal status of a drug. On the other hand, there are no OTC treatments available for the treatment of menorrhagia.

5. EFFICACY

Tranexamic acid is an effective treatment for menorrhagia, and has been found to

reduce blood loss by as much as 40-50%. In a small study more than 50% of women achieved a normal blood loss (i.e. less than 80 mL). Tranexamic acid not only reduces menstrual blood flow but also increases women's quality of life as has been shown by two phase IV studies. In these studies women felt a dramatic improvement in the investigated quality of life parameters (social activities, work, productivity, cleanliness, action radius, and overall functioning).

Assessor's comment:

The efficacy of tranexamic acid in treating menorrhagia is already established as the product is licensed for this indication. The proposed dosage is within the licensed dose for the POM product:

POM posology:

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 4g daily (8 tablets) should not be exceeded. Treatment with Cyklokapon should not be initiated until menstrual bleeding has started.

Proposed P posology:

The recommended dosage is 2 tablets 3 times daily for as long as is needed, but for a maximum of 4 days. If there is very heavy menstrual bleeding, the dosage may be increased. A total dose of 4g daily should not be exceeded. The posology for very heavy menstrual bleeding should be clarified further.

6. SAFETY

Safe use of Cyclo-f as a pharmacy product is dependent on whether or not the POM criteria are met.

6.1 First POM criterion:

The substance is likely to present a direct or indirect danger, even when used correctly, if utilised without medical supervision.

6.1.1 Self-diagnosis of menorrhagia

Whilst there is an objective measurement to define menorrhagia, this is seldom used in practice. In the clinic the diagnosis is based on a woman's subjective assessment of blood loss, despite the fact that there is a poor correlation between this subjective assessment and objective measurement. (See also section 4.1 of this report).

A study discussed in the expert report has attempted to simulate the OTC situation. Patients in a gynaecology waiting room were presented with written information about Cyclo-f, similar to that in the PIL. The study found a good correlation between the woman's self-diagnosis of menorrhagia and the doctor's assessment for eligibility (99%).

Assessor's comment:

There is a discrepancy between the self-diagnosis of menorrhagia by patients and the RCOG guidelines for the management of the condition. Self-assessment would in effect bypass the initial medical assessment and referral process. The guidelines

recommend that an abdominal and pelvic examination be performed in all women complaining of menorrhagia. There is also the recommendation that referral should be considered if patients have symptoms suggestive of other pathology and there are risk factors for endometrial cancer, if the uterus is enlarged, or a pelvic mass present.

Whilst other serious underlying conditions, such as endometrial cancer and cervical cancer, are less likely to be present in patients who have regular periods in the absence of inter-menstrual bleeding and/or post-coital bleeding, examination allows for a chance finding of malignancy and may provide a further opportunity for cervical screening. One possibility in order to bring the management of menorrhagia in the pharmacy setting in line with current clinical guidelines is that patient self-medicate with Cyclo-f only after being seen by their doctor and commenced on tranexamic acid (see also section 10 option 2).

6.1.2 Direct danger

On the basis that the drug is being used correctly, the potential danger arises either directly as a consequence of adverse reactions or indirectly by masking serious underlying pathology.

6.1.2.1 Adverse Reaction Profile

Tranexamic acid, under the trade name Cyklokapron, has been marketed worldwide for 40 years and in the UK for more than 30 years. The adverse reaction profile has therefore been well characterised. The one controversy is whether or not there is an increased risk of thrombosis with tranexamic acid treatment.

It is estimated that since its market introduction the exposure to Cyklokapron for menorrhagia corresponds to 3.2 million women years. In addition, a further 15 million patients have been treated for other indications. More than one million patients have been treated with Cyklokapron solution for injection. Since its introduction as an OTC medicine for menorrhagia in Sweden, 15 million tablets have been sold with an estimated exposure of 64,000 woman years.

The most common adverse reactions consist of: nausea, vomiting, diarrhoea and allergic skin reactions. There have been rare reports of vision disturbances that are reversible when treatment is stopped.

Since 1972 there have been a total of 248 reports on 395 adverse reactions on the ADROIT database. These reports include 13 fatal reactions and 54 thrombosis related events for all formulations of tranexamic acid.

The expert states that “the risk of thromboembolic episodes is not increased by tranexamic acid.” The drug acts by inhibiting fibrinolysis and has no thrombogenic action and does not induce a general prothrombotic state. Thromboembolic disease is not uncommon in women in their fertile years. About half of the episodes of thromboembolic disease are reported to occur without clear, clinically identifiable cause. Tranexamic acid is used widely and the incidence of thromboembolic adverse events reported in association with it is low. From the data available, it is not possible to determine if a casual relationship exists between the use of tranexamic acid and thromboembolic events.

A Cochrane review noted that there were no data available within randomised controlled trials that record the frequency of thromboembolic events. Long-term studies in Sweden have shown that the incidence of thrombosis is comparable to the observed frequency of spontaneous thrombosis in the general population. One case-controlled study in Sweden estimated that the prevalence of tranexamic acid used 1 month prior to the thrombotic event (based on interview) was no higher than in the control group.

One unpublished report discusses 19 years of Swedish experience of tranexamic acid use in menorrhagia estimated to be 238,000 women years. In total 11 cases of thromboembolic events were reported, yielding an annual incidence of 4.6 per 100,000 that was considered to be comparable to that of spontaneously reported incidence in fertile women.

An expert from Preventative Cardiovascular Medicine, Imperial College school of Medicine in 1999 states: “ *Large robust studies are not available to provide, with confidence, an accurate assessment of the risks of thromboembolic disease associated with the use of tranexamic acid. It is feasible on currently available evidence to say with confidence that the population attributable risk associated with the use of tranexamic acid is, if present at all, vanishing small.*”

One can speculate that tranexamic acid is likely to reduce the dissolution rate of a newly formed thrombus, thus increasing the risk of embolism and other clinical consequences. This scenario would be particularly relevant to patients that are also taking oral contraceptives. However in another statement the expert writes: “ *...unless some as yet adverse unidentified mechanistic interaction between the two types of agents occurs, there is no reason to believe that these two agents used together will increase the risk of thromboembolic disease above levels currently associated with the use of combined oral contraceptives.*” The lack of evidence linking an increased risk of thrombosis in patients, undergoing high-risk operations such as hip and knee replacement is put forward as further evidence of lack of thromboembolic effect.

Assessor’s comment:

Under section 4.4 “Special warnings and precautions” of the POM SPC a statement regarding regular eye examinations and liver function tests should be performed in patients on long-term treatment for angioneurotic oedema. There is no such warning in the proposed SPC. Given the short-term use, even if repeated, this is unlikely to be necessary in the SPC for the P product. The PIL advises patients to cease treatment if visual disturbance occurs. This is acceptable.

Thrombosis is a consequence of the interaction of multiple risk factors such as smoking, obesity, Factor V Leiden mutation, oral contraception use etc. There is no evidence to support an association between tranexamic acid use and thromboembolism either alone or in combination with oral contraceptives. However, an incremental risk in individuals who may unknowingly have multiple risk factors cannot be entirely dismissed.

The proposed SPC for Cyclo-f contraindicates use in women at increased risk of thromboembolic disease: active thromboembolic disease, a previous thromboembolic event and a family history of thrombophilia. In view of the known relationship

between combined oral contraceptive use and thromboembolic disease, consideration should be given to adding oral contraceptive use to the list of contraindications or cautions. Such an added precaution is unlikely to exclude many otherwise eligible women from receiving treatment, as menorrhagia is less common in those taking oral contraceptives.

6.1.1.2 Interactions

Tranexamic acid is not dependent on metabolic activation or deactivation. Protein binding is low therefore drug interactions are not likely to be an issue with OTC treatment. The only theoretical potentiation of the risk of thromboembolic events has already been discussed (See section 6.1.2.1 of this report).

6.1.2.3 Special groups

In view of almost exclusive renal excretion, there is a risk of accumulation in the presence of renal impairment necessitating reduction of dosage.

Patients with haematuria due to upper urinary tract pathology who are treated with tranexamic acid have a risk developing ureteric obstruction.

Whilst there is no evidence of a teratogenic effect, pregnant women should not self-medicate with Cyclo-f. Vaginal bleeding in pregnancy requires medical attention.

Tranexamic acid crosses into breast milk and Cyclo-f should not be taken during breastfeeding unless prescribed by a doctor.

Assessor's comment:

Patients with renal insufficiency and haematuria should be excluded from pharmacy supply of tranexamic acid. Pregnancy and lactation have not been adequately addressed under Section 4.6 of the proposed SPC, although they are covered in the PIL (see also section 7.1 of this report).

6.1.3 Indirect danger

Indirect danger may arise by masking a serious underlying pathology. Endometrial cancer and cervical cancer could both present with menstrual dysfunction. Delay in diagnosis could result in transition from a curable stage to an incurable one.

6.1.3.1 Endometrial cancer

Endometrial cancer is more common in postmenopausal women. The incidence of this disease in the age ranges of 30-34, 35-39, 40-44 and 45-49 is 0.8, 2.2, 4.3 and 10.6/100,000 of the population respectively. It usually presents as irregular heavy bleeding or abnormal vaginal bleeding. In Sweden, where tranexamic acid has been available OTC for 8 years, there has been no increase in the reported incidence of endometrial carcinoma.

Assessor's comment:

Obesity, diabetes, nulliparity, family history, polycystic ovary syndrome, unopposed oestrogen treatment, tamoxifen are risk factors associated with endometrial cancer. These are not listed as a caution in the SPC. Cyclo-f is indicated in women with regular periods. The PIL advises women with irregular bleeding and inter-menstrual bleeding to consult their doctor. This list should be expanded further to include risk

factors for endometrial cancer. An age restriction has not been proposed, but in view of the increasing incidence with age, this can be considered (see option 3 in section 10 of this report).

In the proposed SPC there is currently no particular time limit beyond which patients should seek medical attention. However, it can be considered that those women who do not respond to treatment within 3 cycles should seek medical advice and those patients who respond can be allowed to continue Cyclo-f for as long as necessary or until they reach the upper age limit (see option 3 in section 10 of this report).

6.1.3.2 Cervical cancer

Cervical cancer is more common in premenopausal women and most commonly presents with inter-menstrual bleeding and/or postcoital bleeding. Therefore, menorrhagia in patients with regular periods is unlikely to be a sign of cervical cancer. A national screening program is also in place to enable detection.

Assessor's comment:

The PIL informs patients of the importance of inter-menstrual bleeding and post-coital bleeding and stresses that Cyclo-f should only be used in patients with regular heavy periods.

6.1.3.3 Benign intra-uterine disease

Fibroids and polyps are common benign conditions. Approximately 30% of uteri removed because of menorrhagia are found to have fibroids. Polyps are present in approximately 10% of women investigated for menorrhagia.

Fibroids may present with heavy periods. However, the expert report states that neither polyps nor fibroids have been proven to cause menorrhagia. Both are slowly growing and can regress without treatment. A delay in the diagnosis due to self-medication is unlikely to be clinically significant.

6.1.3.4 Anaemia

Menorrhagia may lead to iron-deficiency anaemia that would normally be treated with iron supplementation. A reduction in blood loss is likely to ameliorate the situation although may not be sufficient to normalise Hb levels and treatment of anaemia could be delayed. However, it is likely that the overall effect of changing the status of tranexamic acid would be to reduce the incidence of anaemia in the population as a whole. The proposed PIL advises women with symptoms and signs of anaemia to see their doctor if the symptoms do not improve after commencing treatment with Cyclo-f.

Assessor's comment:

The RCOG guidance recommends that a full blood count should be carried out in all women presenting with menorrhagia. A delay in the diagnosis of anaemia in an otherwise fit woman is unlikely to be of any major consequence. Additionally, it is likely that women with symptoms arising from significant anaemia will consult their doctor anyway.

6.2 Second POM criterion

The substance is frequently used incorrectly and as a result presents a direct or indirect danger to human health.

The applicant considers that tranexamic acid has been used for 40 years and there are only a few reports about incorrect use. Heavy menstrual bleeding is a short-lasting, self-limiting condition where chronic use is unnecessary; therefore the risk for excessive, prolonged use of tranexamic acid must be minimal.

Assessor's comment:

Many women complaining of menorrhagia have loss that is within the normal range. The question is whether there is a possibility of inappropriate use to reduce normal menstrual bleeding. The applicant presented an argument that heavy menstrual bleeding is a subjectively perceived condition and the aim of the treatment with tranexamic acid is not only to decrease menstrual blood flow, but also to improve women's quality of life. In these circumstances incorrect use is unlikely.

On the other hand, clinically important incorrect use would stem from use by those in whom Cyclo-f is not indicated. Of these, misunderstanding relating to what constitutes a regular or irregular period and whether or not other gynaecological symptoms are present or not, is the most relevant as it would lead to delay in the diagnosis of malignancy. The product information together with the pharmacists' training material can be considered as appropriate tools to address incorrect use of the product.

6.3 Third POM criterion

Contains substances or preparations thereof the activity and /or side effects of which require further investigation.

This aspect has been covered under the first POM criteria. Tranexamic acid has been available for many years with significant patient exposure. The safety profile is well characterised. The only concern relates to assessing the risk of thromboembolism. It is possible that Cyclo-f would slow down or impede the resolution of a thrombus that has already formed. However, there does not appear to be any evidence that tranexamic acid increases the risk of thromboembolism.

There is also no evidence that co-administration with oral contraceptives increases the risk over and above that associated with oral contraceptives alone.

Assessor's comment:

Lack of evidence does not completely prove the absence of an increased risk for thromboembolism associated with the use of tranexamic acid. The question is whether any risk would be altered by changing the legal status of the product.

The proposed SPC contraindicates use in those with active thromboembolic disease and a previous thromboembolic event and a family history of thrombophilia.

Consideration needs to be given to contraindicate use of combined oral contraceptives in this population.

6.4 Fourth POM criterion

Is normally prescribed by a doctor to be administered parenterally Cyclo-f is in tablet formulation to be administered orally.

Cyclo-f is in tablet formulation to be administered orally.

7. PRODUCT INFORMATION

The proposed SmPC, label and patient information leaflet have been supplied.

Changes to the product information have been made to reflect the pharmacy supply of the product.

7.1 SmPC

The SmPC has been updated to reflect the pharmacy supply of the product.

7.2 Patient Information Leaflet (PIL)

The proposed leaflet has been subject of a User Testing study and this has been assessed for compliance with the relevant EU guideline. The results of the user testing study demonstrate that further work is necessary; particularly in relation to ensuring key safety messages are understood. An update to the study will be required to resolve the outstanding issues.

8. PHARMACY TRAINING MATERIAL

A pharmacy training manual has been supplied. It aims to provide information on the following:

- describe the normal menstrual cycle and its disturbance to create menorrhagia
- discuss the symptoms and causes of heavy menstrual bleeding
- explain the way in which Cyklo-f works, and its efficacy and safety profile
- give practical guidance for its supply in the pharmacy
- provide questions that should be used to determine the suitability of supplying Cyklo-f both initially and on repeat purchases.

The content is satisfactory, but needs to be updated to reflect the revisions to the product information outlined in the previous section. Views on the material should also be sought from relevant pharmacy professional organisations.

9. DISCUSSION

Menorrhagia affects a significant proportion of the female population and impacts on daily activities and as a result quality of life. There are no OTC products for the treatment of menorrhagia in the UK. Tranexamic acid is efficacious and is recommended in the RCOG guidelines as first line treatment along with mefenamic acid. This product has been safely supplied by pharmacists in Sweden for 8 years.

There are two key issues:

- Is menorrhagia an appropriate indication for self-diagnosis and treatment?
- Is the safety profile of tranexamic acid such that its use other than under medical supervision is acceptable?

Menorrhagia could be a presenting symptom of underlying pathology. There is therefore a risk that treatment could mask serious disease, particularly endometrial carcinoma. There are a number of cautions in the PIL highlighting possible signs and symptoms of other pathology and recommending that women see their doctor prior to initiating treatment. It is possible that the PIL will educate and draw attention to the importance of recognising certain warning signs.

However, based on published guidelines, “best practice” involves all women presenting with menorrhagia to undergo a pelvic and abdominal examination. The question is whether the need for examination, irrespective of whether it is routinely carried out in practice, renders menorrhagia as an inappropriate indication for self-management.

A study discussed in the expert report has attempted to simulate the OTC situation. The study found a good correlation between the woman’s self-diagnosis of menorrhagia and the doctor’s assessment for eligibility. This provides reassurance that with a suitable PIL, women will be able to self-diagnose menorrhagia.

Staging of both cervical and endometrial cancer is directly related to prognosis. Is limiting Pharmacy supply to those women who have consulted their doctor first an option to avoid delaying diagnosis and treatment? This may not be considered necessary in view of the safeguards in the SPC and PIL, together with suitable training for pharmacy provision.

Tranexamic acid has been marketed for almost 40 years, with significant patient exposure. The safety profile is therefore well characterised. However, there has been concern regarding possible increased risk of thromboembolic events. New supporting information has been submitted demonstrating safe use both in a simulated OTC situation and non-prescription availability in Sweden. Based on the clinical expert report and the new information, there is no evidence to support a causal relationship, and if one exists it is very small.

There is the theoretical possibility that an already formed thrombus would not undergo resolution hence aggravating any thromboembolic episode. Patients that are at increased risk of thrombosis are contraindicated in the SPC. Certain patients on combined oral contraceptives also have an increased risk and concomitant oral contraceptive usage is not a contraindication in the SPC and should be considered alongside other known risk factors.

The safeguards in the SPC and PIL are considered sufficient to allow safe use under Pharmacist supervision. The applicant will provide training materials for pharmacists to ensure appropriate use.

10. ADVICE SOUGHT

The Expert Advisory Group (EAG)/Commission may consider that tranexamic acid 500mg can safely be supplied without prescription under the following conditions:

1. Reduction of heavy menstrual bleeding over several cycles in women with regular, 21-35 day cycles with no more than 3 days individual variability in cycle duration.
2. Strength and pharmaceutical form: 500mg tablets
3. Pack size: 18 tablets.

Suitable amendments to the SPC and PIL will also be required.

11. CHM CONSIDERATION

On the 9th November 2006, The Commission also considered this POM to P reclassification for tranexamic acid 500mg Tablets (CYKLO-F) for reduction of heavy menstrual bleeding in women with regular 21-35 day cycles with no more than 3 days individual variability in cycle duration.

The applicant has discussed the following issues concerning pharmacy availability of tranexamic acid:

- Management of menorrhagia in primary care
- Self-diagnosis of menorrhagia with particular regard to misdiagnosing serious underlying pathology such as endometrial and cervical cancer
- Efficacy of tranexamic acid in the management of heavy menstrual bleeding
- Safety profile of tranexamic acid

There are two key issues:

- Is menorrhagia an appropriate indication for self-diagnosis and treatment?
- Is the safety profile of tranexamic acid such that its use other than under medical supervision is acceptable?

The Commission may consider that tranexamic acid 500mg tablets for the reduction of heavy menstrual bleeding over several cycles in women with regular 21-35 day cycles with no more than 3 days individual variability in cycle duration can be safely be supplied without prescription.

It is recommended that women with the following conditions should be excluded from pharmacy supply:

- Active thromboembolic disease
- History of thromboembolic disease and a family history of thrombophilia
- Treatment with warfarin or combined oral contraceptives

It is also recommended that the following patients should consult their doctor prior pharmacy supply:

- Women aged 45 years and above
- If menstrual bleeding is not reduced after 3 menstrual cycles

- Patients who are obese, diabetic or nulliparous
- Patients with polycystic ovary syndrome or a history of endometrial cancer in a first-degree relative
- Women receiving unopposed oestrogen or tamoxifen.

12. ADVICE SOUGHT

CHM also requested a review of the haematological safety of tranexamic acid. Information has been requested from the applicant. The Expert Advisory Group is requested to provide advice at this stage on the thromboembolic safety of tranexamic acid in the proposed indication and treatment population.

13. EAG CONSIDERATION

The Women's Health Expert Advisory Group (WHEAG)

On the 24th April 2007 the WHEAG considered that under the proposed circumstances of use, tranexamic acid could be used safely without the supervision of a doctor and recommended that public consultation may take place.

14. CONSULTATION

A consultation exercise was implemented, whereby a document proposing pharmacy availability of tranexamic acid was issued to various advisory bodies and organisations. The document was circulated on 7th February 2007, with the deadline for comments of 20th March 2007. The responses received were considered by CHM.

15. CHM CONSIDERATION

CHM considered the application in November 2006 and advised the applicant to submit a suitable Pharmacy Risk Management Plan (PRMP) together with the final PIL and Patient Questionnaire.

The safety profile of Cyklo-f discussed under the Safety Specification section of the PRMP is in line with the SPC. The Pharmacovigilance section of the document highlights the main safety issues related to the product. The applicant will submit PSURs at 6-monthly intervals including usage data, and any spontaneous adverse event reports with thromboembolism. Specific risk minimisation measures include Pharmacy Prescribing Protocol, Pharmacists Training Pack, and PIL user testing. The PIL reflects the exclusion and inclusion criteria for pharmacy supply. These are considered acceptable.

The Medicines for Women's Health Expert Advisory Group has considered the application and provided comments on the PIL and Pharmacy Patient Questionnaire. They recommended that obese and nulliparous women should not necessarily be excluded from pharmacy supply. The PIL and Questionnaire have been amended accordingly. These changes will be incorporated into the PRMP as appropriate.

In parallel with this reclassification application, the Pharmacovigilance Signal Management Team identified a signal of retinal vein thrombosis in association with tranexamic acid use and requested the applicant to review all cases of retinal vein and artery occlusion. The applicant identified 14 ADRs reported during the review period

of 27 years with a patient exposure of 5.5 million patients. Based on this review a suitable statement will be incorporated in the SPC.

CHM advised that the applicant should propose a suitable pack size, which provides sufficient cover of one course of treatment at the maximum dose. The applicant has submitted further justification to support the proposed 18-tablet pack size. The applicant states that the rationale for an 18-tablet pack for P supply is based upon the non-prescription use of Cyklo-f in Sweden since mid-1997. The applicant has also referred to a market research study, which is discussed in detail in the assessment report.

On 12th July 2007 The Commission considered that the PRMP and the proposed 18-tablet pack size were acceptable and that Cyklo-f could safely be supplied without medical supervision.

16. CONCLUSION

The MA holder has implemented all the CSM recommendations with regards to the reclassification of the proposed product. The proposed reclassification for pharmacy availability of Cyklo-F-500mg Film Coated Tablets (tranexamic acid) in pack sizes of 18 tablets is acceptable.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type. A clinical expert report has been written by a suitably qualified person and is satisfactory.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Medicinal products containing tranexamic acid have been available in the UK for much more than ten years. Its use is well established with recognised efficacy and acceptable safety.

This product is identical to the cross-reference product, Cykloapron Tablets- 500mg Film Coated Tablets (PL 15142/0130), granted to MEDA Pharmaceuticals Limited on 19th August 2009 following a series of change of ownerships. The product was first authorised on 22nd December 2004 to Viatrix Pharmaceuticals Limited.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with hydrocortisone is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**CYKLO-F-500MG FILM-COATED TABLETS
(TRANEXAMIC ACID)**

PL 19477/0018

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 7th January 1998.
- 2 After initial assessment, advice was sought from the Committee on Human Medicines (CHM) with regards to the Reclassification application. The Committee met in November 2006 issued its advice
- 3 A consultation exercise was implemented in February 2007 and responses received in March 2007.
- 4 Advice was sought from the WHEAG in April 2007.
- 5 The applicant responded to the MHRA's requests, providing further information for the dossier in March 2007, April 2007 and March 2010.
- 6 The application was determined on 31st March 2010

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Cyklo-F-500mg Film-Coated Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Cyklo-fTM 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg Tranexamic acid as the active ingredient.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets.

White, oblong tablets, 8x18 mm, engraved CY with an arc above and below the lettering.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Reduction of heavy menstrual bleeding over several cycles in women with regular, 21-35 day cycles with no more than 3 days individual variability in cycle duration.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route of administration

Oral.

Posology

Cyklo-f therapy is initiated only once heavy bleeding has started. The recommended dosage is 2 tablets 3 times daily for as long as needed, but for a maximum of 4 days. If there is very heavy menstrual bleeding, the dosage may be increased. A total dose of 4 g daily (8 tablets) should not be exceeded.

Cyklo-f can be used as long as periods remain regular and heavy.

Children: Not for use in children under 18 years of age.

Elderly patients: Not recommended for use in the elderly.

4.3 CONTRAINDICATIONS

- Mild to moderate renal insufficiency
- Hypersensitivity to tranexamic acid or any of the excipients
- Active thromboembolic disease
- A previous thromboembolic event and a family history of thrombophilia.
- Haematuria
- Irregular menstrual bleeding
- Patients being administered warfarin or other anticoagulants
- Patients taking oral contraceptives

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should consult their doctor if menstrual bleeding is not reduced after three menstrual cycles.

Women over the age of 45 years should consult their doctor prior to taking Cyklo-f.

The following patients should consult their doctor prior to initiating treatment with Cyklo-f:

- Patients who are obese and diabetic
- Those with polycystic ovary syndrome or a history of endometrial cancer in a first-degree relative
- Women receiving unopposed oestrogen or tamoxifen

Patients who experience visual disturbance should be withdrawn from treatment.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Cyklo-f will counteract the thrombolytic effect of fibrinolytic preparations.

4.6 PREGNANCY AND LACTATIONPregnancy

Cyklo-f is contraindicated in pregnancy. Although there is no evidence from animal studies of a teratogenic effect, the usual caution with use of drugs in pregnancy should be observed.

Tranexamic acid crosses the placenta.

Lactation

Tranexamic acid passes into breast milk to a concentration of approximately one hundredth of the concentration in the maternal blood. An antifibrinolytic effect in the infant is unlikely.

Breastfeeding women should consult their doctor prior to taking Cyklo-f.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None known.

4.8 UNDESIRABLE EFFECTS

Gastrointestinal discomfort is the most common undesirable effect that may occur but disappear when the dosage is reduced.

Frequency of undesirable effects at a dose of 4g/day (MedDRA LLT):

Gastrointestinal disorders

Common ($\geq 1/100$ to $< 1/10$):

Nausea, vomiting diarrhoea

Skin and subcutaneous tissue disordersUncommon ($\geq 1/1,000$ to $< 1/100$)

Allergic skin reactions

Adverse Events:

Other adverse events have been reported with the use of tranexamic acid but the frequency of the reports cannot be estimated from the available data: thromboembolic events, retinal/artery occlusion and impaired colour vision or other visual disturbances.

4.9 OVERDOSE

Symptoms may be nausea, vomiting, orthostatic symptoms and/or hypotension. Initiate vomiting, then stomach lavage, and charcoal therapy. Maintain a high fluid intake to promote renal excretion. There is a risk of thrombosis in predisposed individuals. Anticoagulant treatment should be considered.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

Tranexamic acid is an antifibrinolytic compound which is a potent competitive inhibitor of the activation of plasminogen to plasmin. At much higher concentrations it is a non-competitive inhibitor of plasmin. The inhibitory effect of tranexamic acid in plasminogen activation by urokinase has been reported to be 6-100 times and by streptokinase 6-40 times greater than that of aminocaproic acid. The antifibrinolytic activity of tranexamic acid is approximately ten times greater than that of aminocaproic acid.

A 2001 study involving more than 800 women demonstrated a significant improvement in their quality of life when taking tranexamic acid.

5.2 PHARMACOKINETIC PROPERTIES

Following oral administration, 1.13% and 39% of the administered dose were recovered after 3 and 24 hours respectively. Tranexamic acid administered parenterally is distributed in a two compartment model. Tranexamic acid crosses the placenta, and may reach one hundredth of the serum peak concentration in the milk of lactating women. Tranexamic acid crosses the blood brain barrier.

Following intravenous administration, the biological half-life of tranexamic acid has been determined to be 1.9 hours and 2.7 hours.

5.3 PRECLINICAL SAFETY DATA

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Core

Microcrystalline cellulose (E460)

Hyprolose (E463)

Talc (E553b)

Magnesium stearate (E572)

Colloidal anhydrous silica

Povidone (E1201)

Coating

Methacrylate polymers

Titanium dioxide (E171)

Talc (E553b)

Magnesium stearate (E572)

Macrogol 8000

Vanillin

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs of PVC/PVDC with aluminium foil backing containing 18 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Viartis Pharmaceuticals Ltd
Sherwood House
7 Gregory Boulevard
Nottingham
NG7 6LB
UK

Trading as:

Meda Pharmaceuticals
Regus House
Herald Way
Pegasus Business Park
Castle Donington
Derbyshire
DE74 2TZ
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 19477/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/03/2010

10 DATE OF REVISION OF THE TEXT

31/03/2010

PATIENT INFORMATION LEAFLET

Patient Information Leaflet



Cyklo-f 500 mg film-coated tablets

Tranexamic acid

- Read all this leaflet carefully because it contains important information for you.**
- Cyklo-f is available without prescription. However, you still need to take it carefully to get the best results.
 - Keep this leaflet. You may need to read it again.
 - Ask your pharmacist if you need more information or advice.
 - If any of the side-effects get serious, or if you notice any side effect not listed in this leaflet, please tell your pharmacist.
 - In this leaflet, Cyklo-f 500 mg film-coated tablets will be called Cyklo-f.

In this leaflet:

1. What Cyklo-f is and what it is used for
2. Before you take Cyklo-f
3. How to take Cyklo-f
4. Possible side effects
5. How to store Cyklo-f
6. Further information

1. What Cyklo-f is and what it is used for

Cyklo-f belongs to a group of medicines called anti-fibrinolytics. These are used to control bleeding. When you bleed your body forms clots to stop the bleeding. In some people these clots break down causing too much bleeding. Cyklo-f stops these clots from dissolving and so reduces bleeding.

Cyklo-f is used only when your periods are regular to control heavy menstrual bleeding (see section 2 if you are unsure whether or not your periods are regular). Cyklo-f reduces the amount of blood lost during your period but may not help other symptoms such as period pain.

Heavy menstrual bleeding can cause anaemia (reduction in red blood cells). People with anaemia may be pale and feel tired, weak, dizzy or faint. If you think you may have anaemia, you should see your doctor.

2. Before you take Cyklo-f

How do I know if my periods are heavy?

Your periods are heavy if:

- you bleed through to your clothes or onto bedding at night – called ‘flooding’
- you need to change your sanitary protection every 2 hours or more often
- you need to use double sanitary protection (tampon plus towels)
- you pass large blood clots
- your periods prevent you from doing normal activities, such as going out, working or shopping.

Do not take Cyklo-f if your periods are not heavy.

■ How do I know if my periods are regular?

- Your periods are regular if both of the following apply to you:
 - your menstrual cycle (i.e. the number of days between the 1st day of one period and the 1st day of the next) is between 21 and 35 days long
 - your menstrual cycle is about the same number of days long each time (i.e. does not change by more than 3 days each time).

Do not take Cyklo-f if your periods are not regular.

Do not take Cyklo-f if:

- you are allergic to tranexamic acid or any of the other ingredients in Cyklo-f (listed in section 6)
- you are under 18 years of age
- your periods are irregular
- you are pregnant
- you are taking the combined oral contraceptive (“the pill”)
- you have kidney disease
- you have blood in your urine between your periods
- you have or have ever had a blood clot in your blood vessels (called a “thrombosis”).

See immediately below for the warning signs of a blood clot.

- anyone in your family has suffered from blood clots in their blood vessels
- you are taking medicines to prevent or treat blood clots (e.g. warfarin).

If any of the above applies to you, do not take Cyklo-f.

Warning signs of a blood clot to look out for:

- pains or feelings of heaviness in your chest
- unusual pains or swellings of your arms or one of your legs
- sudden shortness of breath
- fainting
- coughing up blood.

If you experience any of these symptoms you should see your doctor immediately.

Check with your doctor before starting Cyklo-f if:

- you have recently noticed a change in your normal bleeding pattern
- you are over 45 years old
- your mother, grandmother, aunt or sister has suffered from endometrial cancer
- you are diabetic
- you are very overweight (obese)
- you have polycystic ovary syndrome (PCOS)
- you have abnormal bleeding between your periods
- you bleed after sexual intercourse
- you thought you had gone through the menopause, but now you have started bleeding again
- you have pain during sexual intercourse
- you have pain before the start of your period (also known as premenstrual pain)
- you have pelvic pain (pain in the lower abdomen).

Your doctor may prescribe a different medicine which is better for treating your symptoms.

Warning signs of endometrial cancer

Occasionally heavy periods may be due to an abnormality of the lining of the womb. One of the most serious conditions is endometrial cancer. There are almost always other warning signs of endometrial cancer such as:

- irregular periods
- prolonged periods
- abnormal bleeding between periods.

If any of the above applies to you, see your doctor.

Important: Regular AND heavy periods alone are unlikely to be caused by endometrial cancer.

Tell your doctor or pharmacist before starting Cyklo-f if you are taking any of the following medicines:

- the ‘pill’ (a combined oral contraceptive). You must not take Cyklo-f if you are already taking this medicine
- fibrinolytic drugs such as streptokinase (used to dissolve blood clots)
- tamoxifen (a drug used to treat breast cancer)
- an oestrogen
- any other medicine, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Do not take Cyklo-f if you are pregnant as it may cause problems for your unborn baby. If you are breast-feeding, you should ask your doctor for advice before taking Cyklo-f.

3. How to take Cyklo-f

Remember: Cyklo-f should only be taken on the days when your period is heavy. Do not take Cyklo-f before your period has started as it will not work properly. Swallow the tablets whole, with water if needed. Do not take Cyklo-f for more than 4 days during each of your periods.

Adults:

- The usual dose is two tablets taken 3 times a day (e.g. in the morning, afternoon, and evening) for up to 4 days.
- If your bleeding is not reduced, you can take an extra 2 tablets at night.
- Heavy bleeding usually only lasts for the first two days of your period. When the bleeding becomes less, you should reduce the number of tablets you take, for example, to 2 tablets twice a day.
- Do not take more than 8 tablets per day.

Children under 18 years of age:

- Do not give to children under 18 years of age.

Elderly:

- Cyklo-f is not for use in the elderly.

Using Cyklo-f every month

- Cyklo-f may be used every month as long as it continues to reduce your bleeding AND there are no changes in your bleeding pattern.

If Cyklo-f is not working

See your doctor if:

- Your bleeding has not been reduced by Cyklo-f after using it for 3 periods in a row.
- Cyklo-f seems to have stopped working.

If you take more Cyklo-f than you should

If you accidentally take too many Cyklo-f tablets you should contact your doctor immediately, or go to the nearest hospital casualty department.

If you forget to take Cyklo-f

Do not take a double dose to make up for a missed dose. Take your next dose at the usual time.

If you have any further questions on the use of this product, ask your pharmacist.

4. Possible side effects

Like all medicines, Cyklo-f can cause side effects, although not everybody gets them.

Stop taking Cyklo-f and go immediately to hospital if you experience any of the following rare symptoms:

- pain or feelings of heaviness in your chest
- unusual pain or swelling in your arms or legs
- sudden shortness of breath
- fainting
- coughing up blood.

You may have developed a blood clot in your leg or lungs.

Stop taking Cyklo-f and tell your doctor immediately if you experience any of the following rare symptoms:

- problems with your eyesight, especially your colour vision
- a blood clot in the eye. This may cause bleeding in the eye, or a loss of vision
- itchy, red or swollen skin.

Other side effects:

- feeling sick
- being sick
- diarrhoea.

These are usually mild and pass very quickly, but if they continue, stop taking Cyklo-f and tell your doctor or pharmacist.

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

You can help to make sure that medicines remain as safe as possible by reporting any unwanted side effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0800 100 3352 (available between 10 am to 2 pm Monday to Friday) or fill in a paper form available from your local pharmacy.

5. How to store Cyklo-f

Keep out of the reach and sight of children.

Do not use Cyklo-f after the expiry date stated on the carton and blister foil. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Medicines should not be disposed of via wastewater or household waste. Return any medicine you no longer need to your pharmacist.

6. Further information**What Cyklo-f contains:**

- The active substance is tranexamic acid. Each tablet contains 500 mg tranexamic acid.
- The other ingredients are microcrystalline cellulose (E460), hypolose (E463), talc (E553b), magnesium stearate (E572), colloidal anhydrous silica, povidone (E1201), methacrylate copolymer, titanium dioxide (E171), macrogol 8000 and vanillin.

What Cyklo-f looks like

Cyklo-f tablets are white, oblong film-coated tablets. They are marked with CY with an arc above and below the lettering. They come in packs of 18 tablets.

Marketing Authorisation Holder

Meda Pharmaceuticals, Skyway House, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK.

Manufacturers

MEDA Manufacturing GMBH, Neurather Ring 1, 51063 Cologne, Germany.

This leaflet was last updated on <approval date>

If this leaflet is difficult to see or read, or you would like it in a different format, please contact Meda Pharmaceuticals, Skyway House, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK.

LABELLING

Carton

