COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tranexaminezuur Midas 1000 mg, coated granules in sachet (tranexamic acid)

NL/H/6283/001/DC

Date: 18 June 2026

This module reflects the scientific discussion for the approval of Tranexaminezuur Midas 1000 mg, coated granules in sachet. The procedure was finalised on 12 February 2026. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GFR	Glomerular Filtration Rate
HMB	Heavy Menstrual Bleeding
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
OTC	Over The Counter
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tranexaminezuur Midas 1000 mg, coated granules in sachet, from Midas Pharma GmbH.

The product is indicated in the reduction of heavy menstrual bleeding (menorrhagia) over several cycles in women with regular, 21-35 day cycles with no more than 3 days individual variability in cycle duration.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application using as reference product the European Reference Product (ERP) Cyklo-f 500 mg, film-coated tablets, which has been registered by Pharmacia B.V in Sweden via a decentralised procedure (SE/H/0176/001) since 31 January 1997.
The justification to use this product is based on information received from Sweden.
Tranexaminezuur Midas 1000 mg, is claimed to be therapeutically equivalent to the reference medicinal product Cyklo-f of Sweden. The pharmaceutical form and strength of Tranexamic acid Midas 1000 mg are different from Cyklo-f. The MAH applies for a similar indication and posology and also requests for a non-prescription classification status, in line with the reference product. For this medicine product an over-the-counter (Pharmacies Only 'UA') status has been granted for the 12 sachets pack size in the Netherlands. The other pack sizes will not be marketed in the Netherlands.

The concerned member state (CMS) involved in this procedure was Germany.

Of note, the non-prescription status is a national competence and only requested in the Netherlands and not in Germany

II. QUALITY ASPECTS

II.1 Introduction

Tranexaminezuur Midas are white to off-white coated granules in sachet. Each sachet contains as active substance 1000 mg of tranexamic acid.

The excipients are: sugar spheres (sucrose, maize starch), povidone K30 (E1201), sucralose (E955), silica colloidal anhydrous (E551), polyacrylate dispersion 30 per cent, and talc (E553B).

The coated granules are packed in low-density polyethylene (LDPE)/aluminium/paper sachets. The sachets are packed in carton boxes.

II.2 Drug Substance

The active substance is tranexamic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder and is freely soluble in water. Tranexamic acid contains two chiral centres. The active substance is consistent in X-ray powder diffraction (XRPD) spectrum. The Drug substance specification includes test for Identification (InfraRed) in accordance with the Ph.Eur.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted. Therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional tests for particle size and microbial quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for seven batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. Compatibility studies of the active substance and the proposed excipients have been performed. Since the reference product (Cyklo-f) has a different pharmaceutical form than Tranexaminezuur Midas, previous experience in the development of another drug product in sachets, registered in Europe, was used for proper

selection of excipients, their grade, manufacturing process and parameters selection. Effects of active substance particle size and Eudragit concentration on the dissolution were studied.

Manufacturing process

The main process consists of drug layering on sugar sphere beads using a spraying process, application of a taste masking layer and lubrication of the pellets. Sieving and drying steps are performed in between the layering steps. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average filled weight, uniformity of dosage units (by content uniformity), loss on drying, residual solvents, dissolution, related substances, assay and microbial limit tests. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three batches stored at 25°C/60% RH (36 months), 30°C/65% RH (24 months), 30°C/75% RH (24 months), and 40°C/75%RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light (inside and outside the primary packaging). On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tranexaminezuur Midas has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

For the Ecotoxicity/environmental risk assessment, the MAH has submitted the following study results in line with EMEA/CHMP/SWP/4447/00 Rev. 1- Corr guideline.

Summary of main study results

A GLP compliant readily biodegradability test with tranexamic acid (purity 97%) was performed using the Closed Bottle test.

Substance	Sludge type	Sludge [mL/L]	T [°C]	pH	Duration [d]	biodegradation [%]	Conclusion	Ri
Tranexamic acid	Municipal STP	1.9	20±1	7.6	28	83.3	readily biodegradable	1

All validity criteria for the test were fulfilled. Oxygen depletion in the inoculum blank did not exceed the threshold of 1.5 mg dissolved oxygen/L after 28 days; the measured value was 0.76 $mg \cdot L^{-1}$. At no point did the residual oxygen concentration in the test bottles fall below 0.5 mg/L, with the lowest recorded value being 3.16 $mg \cdot L^{-1}$. The difference between the extreme values of replicate removal of the test chemical at plateau, at the end of the test, or at the end of the 10-day window, was less than 20%. In addition, the percentage degradation of the reference compound exceeded the required level of 60% by day 7 based on ThOD and by day 5 based on COD. In the toxicity control, more than 25% degradation was observed within 14 days, specifically, 45.5% based on ThOD and 51.9% based on COD. Therefore, it can be concluded that the test substance did not exhibit inhibitory effects under the test conditions. Biodegradation of the test substance was 83.3% based on ThOD and 101.5% based on COD. Based on the above results, it was concluded that tranexamic acid is readily biodegradable.

Conclusions on studies:
Tranexamic acid is not considered a PBT substance, it is a readily biodegradable non-natural peptide. Considering the above data, tranexamic acid is not expected to pose a risk to the environment, the environmental risk assessment can be concluded in Phase I.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of the ERP reference product Cyklo-f which is available on the European market. Reference was made to the preclinical data obtained with Cyklo-f. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tranexamic acid is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
Additionally, the MAH has performed a bioequivalence study.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tranexaminezuur Midas 1000 mg, coated granules in sachet (Midas Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Cyklo-f 500 mg, film-coated tablets (Viatris AB, Sweden).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

<u>Bioequivalence study 21-VIN-0007</u>
Design
A balanced, open label, single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-45 years. Each subject received a single dose (1000 mg) of one of the two tranexamic acid formulations. The tablets or granules were orally administered with 240 ml water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.50, 6, 7, 8, 12, 18, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. As the product is an immediate release formulation that can be taken with or without reference to food, bioequivalence/comparative under fasting conditions are considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects were withdrawn from the study due to adverse events (vomiting), one subject withdrew consent, and one subject was withdrawn due to being found positive in drugs of abuse test. The remaining 32 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tranexamic acid, 1000 mg under fasted conditions.

Treatment N=32	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	96 ± 27	100 ± 27	14 ± 4	2.33 (1.50 – 4.00)
Reference	96 ± 25	99 ± 26	14 ± 3	2.33 (1.25 – 4.33)
***Ratio (90% CI)**	0.99 (0.94 – 1.06)	-	1.00 (0.94 – 1.06)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tranexaminezuur Midas is considered bioequivalent with Cyklo-f.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tranexaminezuur Midas. At the time of approval, the most recent version of the RMP was version 0.1 dated 6 January 2025.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cyklo-f. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product.
The MAH provided an adequate review of published clinical data. In addition, the MAH presented adequate bibliographical data to describe an overview of general pharmacodynamic, safety and efficacy properties of tranexamic acid. Overall, the efficacy of oral tranexamic acid in the requested indication of heavy menstrual bleeding and the use in clinical practice is well known and currently well-established since several decades. The safety of oral tranexamic acid in this indication is generally well characterised and most discrepancies with the SmPC of the reference product Cyklo-f are well justified and can be considered supported.

Given the fact that the proposed strength (1000 mg) deviates from the strength of the reference product (500 mg), which can lead to dosing differences, additional dosing recommendations for patients with renal impairment were implemented in the SmPC. The warning concerning visual disturbances in section 4.4 of the SmPC is considered acceptable.

Risk management is adequately addressed. This hybrid other medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Nexag 1 g, coated granules NL/H/5588/001/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tranexaminezuur Midas 1000 mg, coated granules in sachet has a proven chemical-pharmaceutical quality and is a hybrid form of Cyklo-f 500 mg, film-coated tablets. Cyklo-f is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

Cyklo-f exists as non-prescription product in the requested indication in Sweden since 1997. The product with this single indication of menorrhagia is also licensed in the UK with a non-prescription classification status prior to Brexit.
The MAH requested that, as equivalent product to Cyklo-f, Tranexaminezuur Midag 1000 mg, coated granules in sachet can also safely be registered as non-prescription product in EU.
The criteria as laid down in the European Commission Guideline on changing the classification for the supply of a medicinal product for human use (European Commission, 2006 revision) apply, which consists of four criteria and other considerations. This is in line with the CMDh Best Practice Guide for authorisation of Non-Prescription Medicines in the Decentralised and Mutual Recognition Procedures.
The four criteria and other considerations to classify a medicinal product as "*subject to medical prescription*" are described and weighed by the MAH. The MAH stated that Tranexaminezuur Midag 1000 mg does not meet these criteria and therefore confirms that its product can be classified as "not be subject to medical prescription".

The MAH intends to market only the 12 sachets pack size as OTC in The Netherlands. The other pack sizes (24, 36, 48 and 72 sachets) will not be marketed in The Netherlands. With the commitment that the pack sizes 24, 36, 48 and 72 sachets will not be marketed in The Netherlands, this is deemed acceptable and an over-the-counter (Pharmacies Only 'UA') status has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered essential similarity has been demonstrated for Tranexaminezuur Midas with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 February 2026.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.