COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nexag 1000 mg, coated granules in sachet (tranexamic acid)

NL/H/5588/001/DC

Date: 6 January 2026

This module reflects the scientific discussion for the approval of Nexag 1000 mg, coated granules in sachet. The procedure was finalised on 25 October 2023. 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
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 Nexag 1000 mg, coated granules in sachet from Cemag Care.

The product is indicated for: 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. The pharmaceutical form and strength of Nexag 1000 mg coated granules are different from the European reference product (500 mg film-coated capsules).

In this decentralised procedure, therapeutic equivalence is proven between the new product and a European Reference Product (ERP), Cyklo-f 500 mg film-coated tablet, which has been registered in Sweden via decentralised procedure since 31 January 1997. This product is also licenced in the UK with an non-prescription classification status prior to Brexit.

A repeat-use procedure (NL/H/5588/001/E/001) was used to register the product in Belgium, Estonia, Hungary, Lithuania, Latvia, Poland and Romania.

The concerned member states (CMS) involved in this procedure were France, Italy, Portugal, Spain and Sweden.

For this application, scientific advice has been given by the MEB.

OTC (over the counter) status was requested by the MAH and accepted by the MEB. The MAH applies for the same indication and posology and also requests for a non-prescription classification status, in line with the Swedish reference product.

II. QUALITY ASPECTS

II.1 Introduction

Nexag are white to off-white coated granules and contain 1000 mg of tranexamic acid as the active substance.

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

The 1750 mg granules are packed in a sachet (low density polyethylene/aluminium/low density polyethylene/paper). One box contains 12 sachets.

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 has two chiral centers. No reference on polymorphism is found but the product produced is consistent in XRPD (X-Ray Powder Diffraction) spectrum.

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
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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.

Compatibility studies of the active substance and the proposed excipients have been performed. Since the reference product (CYKLO-F 500 mg tablets) has a different pharmaceutical form than the proposed product, the Applicant's previous experience in the development of Secnidazole sachets 2 g, 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. The products used in the bioequivalence study are acceptable. The dissolution profile, assay and impurity profile of the biobatch and reference product as used for the clinical studies are

comparable. The developed QC dissolution method is acceptable. The packaging is usual and suitable for the product at issue.

Manufacturing process
The manufacturing process consists of sieving, layering and dying. The 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 (HPLC and IR), 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 from three batches stored at 25°C/ 60% RH (24 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 24 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 Nexag 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)

Since Nexag is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a formulation of Cyklo-f which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. 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. The member states agreed that no further clinical studies are required, besides the bioequivalence/comparative bioavailability study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioavailability study in which the pharmacokinetic profile of the test product Nexag 1000 mg (Athena Drug Delivery Solutions Pvt. Ltd., India) was compared with the pharmacokinetic profile of the reference product Cyklo-f 500mg film coated tablet (Meda AB, Sweden).

The choice of the reference product in the bioavailability study has been justified by comparison of dissolution study (pH 0.1, 4.5 and 6.8) results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioavailability study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover, open label, balanced bioequivalence/comparative bioavailability study was carried out under

fasted conditions in 36 healthy male subjects, aged 19-45 years. Each subject received a single dose (1000 mg Nexag or 2x 500 mg Cyklo-f) of one of the two tranexamic acid formulations. The tablet was orally administered with 240 mL water after an overnight fast 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, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 12, 18, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Tranexamic acid may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of tranexamic acid. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
36 subjects were enrolled in the study. One subject withdrew from period I due to an adverse event (vomiting). Three subjects withdrew in period II; one withdrew consent, one due to an adverse event (vomiting), one was positive for drug abuse. 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	96.3 ± 27.0	99.9 ± 27.3	14.2 ± 3.7	2.33 (1.5 – 4.0)
Reference	96.4 ± 25.3	99.3 ± 26.1	14.2 ± 3.3	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence/comparative bioavailability study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nexag 1000 mg coated granules in sachet is considered bioequivalent with Cyklo-f 500 mg film-coated tablet.

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 (version 0.3 signed 18 Augustus 2023), 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 Nexag.

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. MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

An adequate review of published clinical data has been shown between the oral immediate-release formulations Nexag 1000 mg coated granules and Cyklo-f 500 mg tablets. 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 characterized and the 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 justification of Nexag 1000 mg coated granules in sachet provided for non-prescription/OTC classification has been assessed by following 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) to classify a medicinal product as "subject to medical prescription". It can be concluded that, based on the justification provided, the all criteria and the "other considerations" do not apply for this medicinal product in the requested indication. The currently presented justification in support of a non-prescription classification for Nexag 1000 mg coated granules in sachet is therefore currently acceptable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The study was performed in English.

The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nexag 1000 mg, coated granules in sachet has a proven chemical-pharmaceutical quality and is a form of Cyklo-f 500 mg film-coated tablet. 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.

In the 1006th Board meeting of 30 June 2022, the following was discussed: MAH's request for an OTC (over the counter) status for the product. At present, tranexamic acid is only available by prescription in the RMS. The reference product has had OTC status since 1997 in Sweden. The RMS is concerned about the pro-thrombotic effect of the product, although there are no safety studies which suggest this may be a risk, as well no indication of this being a risk with the reference product in Sweden. Furthermore, the RMS requires medical supervision to investigate the cause of the heavy menstrual bleeding, as indicated in the Product Information. The Product Information also indicates that a doctor should be consulted if the symptoms become irregular or last longer than two weeks.

In the 1027th Board meeting of 4 May 2023 the conclusion was reached that the product would receive OTC status. The MAH provided clinical literature studies which demonstrated the low or no risk of pro-thrombotic effect of oral tranexamic acid, as well as restating the experiences of similar products in other countries.

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 that essential similarity has been demonstrated for Nexag 1000 mg, coated granules in sachet with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 2023.

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
NL/H/5588/ 001/IA/001	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No	14-12-2023	Approved	N/A
NL/H/5588/ 001/IB/002	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Implementation of an agreed wording, no new data submitted.	Yes	13-4-2024	Approved	N/A
NL/H/5588/ P/001	Artikel 61(3): changes to patient information	Yes	22-7-2024	Approved	N/A
NL/H/5588/ 001/IA/003	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability; for an active substance; for a starting material/reagent/intermediate used in the manufacturing process of the active substance; for an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph o Updated certificate from an already approved manufacturer	No	14-1-2025	Approved	N/A
NL/H/5588/ 001/IB/004	Change in the shelf-life or storage conditions of the finished product • Extension of the shelf life of the finished product o As packaged for sale (supported by real time data)	Yes	14-3-2025	Approved	N/A
NL/H/5588/ 001/E/001	Repeat Use – BE, EE, HU, LT, LV, PL and RO		29-7-2025	Approved	N/A
NL/H/5588/ 001/IA/006	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a site where batch control/testing takes place	No	3-11-2025	Approved	N/A