COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Colchicine Strides 0.5 mg tablets (colchicine)

NL/H/5288/001/DC

Date: 29 September 2022

This module reflects the scientific discussion for the approval of Colchicine Strides 0.5 mg tablets. The procedure was finalised at 29 June 2022. 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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
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 Colchicine Strides 0.5 mg tablets, from Strides Pharma (Cyprus) Limited.

The product is indicated for:

Adults
Colchicine is used for the treatment of acute gout.
Colchicine is also used for the prophylaxis of recurrent gout and to prevent acute attacks during the initial treatment with allopurinol or uricosuric drugs.

Adults and paediatric patients
Colchicine is indicated in Familial Mediterranean Fever (FMF) for prophylaxis of attacks and prevention of amyloidosis.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Colchicine Tiofarma 0.5 mg tablets (NL RVG 21347) which has been registered in the Netherlands by Tiofarma B.V. since 28 December 1998 through MRP NL/H/3863/001/MR.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Colchicine Strides is a white, round tablet debossed with “C5” on one side and plain on the other side. Each tablet contains 0.5 mg colchicine.

The tablets are packed in white opaque PVC-aluminium blisters.

The excipients are: lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycolate, povidone K30 (E1202) and magnesium stearate (E470b).

II.2 Drug Substance

The active substance is colchicine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is a yellowish-white amorphous or crystalline powder that is soluble in water, freely soluble in alcohol and chloroform and slightly soluble in ether. A single polymorphic, crystalline form is consistently produced. The active substance is dissolved during the drug manufacturing process; therefore, the initial form is not critical.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of several stages in which the active substance is extracted from *Gloriosa superba* seeds. No class 1 organic solvents are used in the manufacturing process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

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. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for 23 batches stored at 25°C/60% RH (up to 60 months), 30°C/65% RH (up to 60 months) and 40°C/75% RH (6 months) which is in accordance with applicable European guidelines. No significant changes were observed. Based on the data submitted, a retest period could be granted of 36 months when stored in tight, light-resistant containers below 30°C.

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 explained. The choice of the manufacturing process is adequately justified. The quality control dissolution test and specifications are based on the monograph of the British Pharmacopoeia for colchicine tablets. A study on the polymorphic form was conducted and the results confirm the consistency of the polymorphic forms over

the manufacturing process. One bioequivalence (BE) study was performed against the 0.5 mg reference product and considered representative.

Manufacturing process

The product is manufactured using a conventional wet-granulation manufacturing process comprised of sifting, preparation of the colchicine solution, mixing, granulation, drying, sifting and compression of the tablets. Description of the process and critical steps are described in sufficient detail. Given the low content of the active substance the manufacturing process is not considered to be a standard process. The appropriate European guideline states that therefore production scale validation data should be provided of each batch size. These data have been provided and the results indicate that the process is consistent.

Control of excipients

All excipients comply with the Ph. Eur. requirements.

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 appearance, identification, assay, water content, average mass, dissolution, content uniformity, related substances, residual solvents and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scaled 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 for three production scaled batches stored under long-term stability conditions at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). This in accordance with applicable European guidelines. Colchicine must be protected from light, therefore photostability studies were performed on lab scale batches. These studies indicate that the blister kept in the carton is sufficient to protect from light, however a post-approval commitment is given to perform the photostability studies with commercial batches. On the basis of the data submitted a shelf life of two years was granted. The labelled storage conditions are to keep the blister in the outer carton in order to protect from light.

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

No materials derived from animal origin except lactose monohydrate are used in the manufacturing of the tablets. TSE/BSE certificates for the active substance and excipients are provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitment was made:

- The MAH will perform a photostability study on commercial scale batches within one month after closure of this procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Colchicine Tiofarma 0.5 mg tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Colchicine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Colchicine Strides 0.5 mg tablets (Strides Pharma (Cyprus) Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Colchicine Tiofarma 0.5 mg tablets (Tiofarma B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male and female subjects, aged 18-38 years. Each subject received a single dose (0.5 mg) of one of the two colchicine 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 twelve days.

Blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The wash-out of 12 days is long enough, since the elimination half-life is 30-60 minutes. Colchicine is not recommended to be taken with food. Therefore, a study under fasted conditions is appropriate. 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

Three subjects did not report to the facility or withdrew consent for period II. Therefore, a total of 57 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of colchicine 0.5 mg under fasted conditions.

Treatment N=57	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	14.86 ±4.82	2.36 ±0.85	1.0 (0.5 – 4.0)
Reference	14.87 ±5.39	2.43 ±0.95	1.0 (0.5 – 2.3)
***Ratio (90% CI)**	1.01 (0.95 – 1.08)	1.07 (0.99 – 1.16)	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study

The acceptance ranges of 0.80 – 1.25% for C_{max} and 0.90-1.11% for AUC_{0-t} are in accordance with the product-specific guidance for colchicine and both confidence intervals are within the bioequivalence acceptance range. Based on the submitted bioequivalence study Colchicine Strides 0.5 mg is considered bioequivalent with Colchicine Tiofarma 0.5 mg.

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 Colchicine Strides.

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

Important identified risks	-
Important potential risks	-
Missing information	-

There are no important identified risks, important potential risks and missing information identified for Colchicine Strides. 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 Colchicine Tiofarma 0.5 mg tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is like the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with four 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

Colchicine Strides 0.5 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Colchicine Tiofarma 0.5 mg tablets. Colchicine Tiofarma 0.5 mg 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.

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 Colchicine Strides with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 June 2022.

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