COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Colchicine Ria 0.5 mg and 1 mg tablets

(colchicine)

NL/H/4121/001-002/DC

Date: 11 February 2019

This module reflects the scientific discussion for the approval of Colchicine Ria 0.5 mg and 1 mg tablets. The procedure was finalised at 25 February 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
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 Ria 0.5 mg and 1 mg tablets from RIA Generics Limited.

The product is indicated for:

Adults
- Treatment of acute gout when prostaglandin synthetase inhibitors are contraindicated or not tolerated by the patient.
- Prophylaxis of gout attack, during initiation of uric acid -lowering therapy, when prostaglandin synthetase inhibitors are contraindicated or not tolerated by the patient.

Adults and paediatric patients (children under 1 year, children and adolescents)
- Colchicine is indicated in familial Mediterranean fever for the prophylaxis of seizures and prevent amyloidosis.

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

The decentralised procedure for the 0.5 mg strength concerns a generic application claiming essential similarity with the innovator product Colchicine Teva 0.5 mg tablets (NL Licence RVG 34100) which has been registered in The Netherlands by Teva Nederland B.V. since 12 October 2006 (original product).
The 1 mg strength is filed in as hybrid application with reference to the authorisation of Colchicine Teva 0.5 mg tablets.

The concerned member states (CMS) involved in this procedure were Malta (0.5 mg strength) and Spain (1 mg strength).

The marketing authorisation for the 0.5 mg strength has been granted pursuant to Article 10(1) of Directive 2001/83/EC. For the 1 mg strength the marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a so called hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Colchicine Ria is a white to off white round shaped, biconvex uncoated tablet that is available in two strengths:
- Colchicine 0.5 mg tablets are debossed with ‘L’ on one side and plain on other side.
- Colchicine 1mg tablets are debossed with “H” on one side and plain on the other side

And contains as active substance 0.5 mg and 1 mg of colchicine.

The tablets are packed in blisters of PVC/PVDC with aluminium foil.

The excipients are lactose monohydrate, pregelatinised starch, sodium starch glycolate, purified water, colloidal anhydrous silica, ethanol 96%, and stearic acid.

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is colchicine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Colchicine is a yellowish-white powder. It is very soluble in water, freely soluble in ethanol and practically insoluble in cyclohexane. No test for particle size or polymorphic form is required since colchicine will be dissolved.

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. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

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. the choice of active substance and excipients has been explained. Novel excipients are not used.

A bioequivalence study with the 0.5 mg strength was conducted to demonstrate similarity in vivo. Biowaiver of strength is applied for the 1 mg tablet. The provided dissolution data at three pH's support the biowaiver of strength.

Manufacturing process

The manufacturing process includes sifting of material, binder solution preparation (this includes colchicine), dry mixing and granulation, drying of granules, sifting and milling, blending and lubrication, compression and packaging. The manufacturing process is a non-standard process. Description of the process and critical steps are in sufficient detail. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient batches in accordance with the relevant European guidelines.

Control of excipients

The used excipients are of Ph.Eur. quality. 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 weight of tablet, loss on drying, water content, hardness, uniformity of dosage units, dissolution, assay, related substances, microbial limits, and residual solvents. 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 batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

24 months long term (25°C/60% RH) and six months accelerated storage (40°C/75% RH) stability data are provided of the 0.5 mg and the 1.0 mg tablets. The stability studies are in line with the ICH guidance. Photostability studies demonstrated that the tablets are sensitive for light. On basis of the data submitted, a shelf life was granted of 24 months. Store in the original container protected from light.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Colchicine Hetero 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 Colchicine Hetero 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 Teva 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 Ria 0.5 mg tablets is compared with the pharmacokinetic profile of the reference product Colchicine 0.5 mg PCH tablets (Pharmachemie BV, The Netherlands).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for 1 mg tablet is granted based on the following:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the strengths is the same.
- The composition of the strengths are quantitatively proportional.
- Colchicine exhibits linear pharmacokinetics within the clinical dose range of 0.5 mg to 1.5 mg.
- Comparative dissolution tests were performed in purified water, 0.1N HCL, pH 4.5 acetate buffer and pH 6.8 phosphate buffer at 100 rpm using basket apparatus. At all pH levels, the dissolution was more than 85% in 15 minutes. The dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male/female subjects (mean age 27.6 years). Each subject received a single dose (0.5 mg) of one of the 2 colchicine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected at 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. The sampling times and the wash-out period are considered sufficient.

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.

Colchicine is a drug with a narrow therapeutic index. Therefore CI limits for AUC_{0-72} are restricted to 90-111% whereas C_{max} limits can be allowed for 80-125% for the assessment of bioequivalence (EMA/CHMP/494830/2018 Rheumatology Immunology Working Party (RIWP) response to CMDh questions).

Results

Two subjects did not report to the clinical facility for period II check in and hence they were considered as dropout from the study. Therefore 54 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=54	**AUC_{0-t}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	19.97 ± 6	2.65 ± 1	1.00 (0.5 - 3.0)
Reference	19.52 ± 5	2.40 ± 1	0.83 (0.5 - 1.75)
***Ratio (90% CI)**	1.01 (0.95 – 1.08)	1.08 (0.99 – 1.18)	--
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 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.90 – 1.11 and 0.80 – 1.20. Based on the submitted bioequivalence study Colchicine Ria is considered bioequivalent with Colchicine 0.5 mg PCH tablets.

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 Ria.

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

Important identified risks	• Bone marrow depression with agranulocytosis and aplastic anemia • Myopathy, Rhabdomyolysis
Important potential risks	• Potential for medication errors • Potential for harm of overdose
Missing information	• Use in pregnancy • Use during lactation • Use in men with child wish

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 Teva. No new clinical studies were conducted. The 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 and hybrid medicinal product can be used instead of the reference product.

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 regarding content and safety messages to Colchicine 500 microgram tablets (Renata (UK) Limited; PL 42765/0002) and regarding font style size, format and lay-out to Sertraline 50 mg and 10 mg film-coated tablets (NL/H/3452/001-002/DC; Ria Generics; NL Licence RVG 117160-3). 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

Colchicine Ria 0.5 mg and 1 mg tablets has a proven chemical-pharmaceutical quality. The 0.5 mg strength is a generic form of Colchicine Teva 0.5 tablets. The 1 mg strength is a hybrid form. Colchicine Teva 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 Ria with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 February 2019.

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/4121/001-002/IB/001	Update of texts in line with reference product	--	6-12-2019	Approval	--