Public Assessment Report
Decentralised Procedure
Colchicine 500 microgram Tablets
(colchicine)

Procedure No: UK/H/5726/001/DC
UK Licence No: PL 30306/0573

Actavis Group PTC ehf.
LAY SUMMARY

Colchicine 500microgram Tablets
(colchicine, tablet, 500microgram (mcg))

This is a summary of the Public Assessment Report (PAR) for Colchicine 500microgram Tablets (PL 30306/0573; UK/H/5726/001/DC). It explains how Colchicine 500microgram Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Colchicine 500microgram Tablets.

This product will be referred to as Colchicine Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Colchicine Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Colchicine Tablets and what are they used for?
Colchicine Tablets is a ‘generic medicine’. This means that Colchicine Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands).

Colchicine Tablets are used to treat gout attacks in adults. They are also used to prevent flare-ups of gout in adults when treatment is started with other drugs such as allopurinol, probenecid and sulfinpyrazone.

How do Colchicine Tablets work?
Gout causes attacks of painful inflammation in one or more of the patient’s joints. It is caused by a build-up of a naturally-occuring chemical in the blood called uric acid (urate). From time to time the level of uric acid in the patient’s blood may become too high and tiny grit-like crystals may form which typically collect in the patient’s joints and tendons. The crystals irritate the tissues of the joint causing inflammation, swelling and pain. Colchicine Tablets contains the active ingredient colchicine, which belongs to a group of medicines called anti-gout agents. These medicines work by reducing the number of white blood cells which travel into the inflamed areas. This helps to break the cycle of inflammation and reduces swelling and pain.

How are Colchicine Tablets used?
The pharmaceutical form of Colchicine Tablets is a tablet and the route of administration is via the mouth (oral).

The patient must always take this medicine exactly as their doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure.

The patient’s doctor will tell the patient how many tablets to take and for how long. Colchicine Tablets should be swallowed whole with a glass of water.

Use in adults
Dose to treat gout attack:
The recommended dose is two Colchicine Tablets to start followed by one Colchicine Tablet after one hour. No further tablets should then be taken for 12 hours. If necessary, treatment with Colchicine Tablets can then resume with a maximum dose of one tablet three times daily until symptoms are relieved. The course of treatment should end when symptoms are relieved or when a total of twelve Colchicine Tablets have been taken. The patient should not take more than twelve Colchicine Tablets as
a course of treatment. After completion of a course of Colchicine Tablets, the patient should not start another course for at least three days.

**Dose to prevent flare-ups of gout when treatment is started with other drugs:**
The recommended dose is one Colchicine Tablet twice daily. The patient’s doctor will tell the patient how long their treatment with Colchicine Tablets will last.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Colchicine Tablets have been shown in studies?**
Because Colchicine Tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Colchicine Tablets?**
Because Colchicine Tablets is a generic medicine and is bioequivalent to the reference medicine Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Colchicine Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Colchicine Tablets approved?**
It was concluded that, in accordance with EU requirements, Colchicine Tablets has been shown to have comparable quality and to be bioequivalent to Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands). Therefore, the MHRA decided that, as for Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands); the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Colchicine Tablets?**
A risk management plan (RMP) has been developed to ensure that Colchicine Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Colchicine Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Colchicine Tablets
Denmark, Finland, Iceland, Norway, Poland, Sweden, and the UK agreed to grant a Marketing Authorisation for Colchicine Tablets on 13 March 2015. A Marketing Authorisation was granted in the UK on 07 April 2015.

The full PAR for Colchicine Tablets follows this summary.

For more information about use of Colchicine Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
TABLE OF CONTENTS

I Introduction Page 6
II Quality aspects Page 7
III Non-clinical aspects Page 9
IV Clinical aspects Page 9
V User consultation Page 12
VI Overall conclusion, benefit/risk assessment and recommendation Page 12

Annex 1 - Table of content of the PAR update for MRP and DCP Page 15
I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Colchicine Tablets ((PL 30306/0573; UK/H/5726/001/DC) could be approved. The product is a prescription-only (POM) medicine indicated in adults for:

- Treatment of acute gout
- Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Denmark, Finland, Iceland, Norway, Poland and Sweden as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Colchicine tabletten, 0.5 mg Tablets, which was originally granted to TioFarma BV, in the Netherlands on 28 December 1998.

Colchicine is a tricyclic alkaloid. It exists in two forms (-)-(aS,7S)-colchicine and (+)-(aR,7S)-colchicine, which interconvert quickly when the compound is in solution (ratio of the two conformers is 99:1). Colchicine is used for the treatment of acute gout and for short term prophylaxis during initial therapy with allopurinol and uricosuric drugs. The precise mode of action of colchicine is not well understood, but it is thought that colchicine causes the inhibition of the migration of granulocytes into the inflamed area. This reduces the release of lactic acid and proinflammatory enzymes that occurs during phagocytosis and breaks the cycle that leads to the inflammatory response.

One bioequivalence study was submitted to support this application comparing the applicant’s test product Colchicine Tablets (Actavis Group PTC ehf) with the reference product Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands) under fasting conditions. The applicant has stated that the bioequivalence study were conducted in compliance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the subject of this application is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 500 micrograms of the active ingredient, colchicine. Other ingredients consist of the pharmaceutical excipients, lactose monohydrate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate and magnesium stearate. The finished product is packed into white opaque polyvinyl chloride (PVC)/plain push through aluminium foil blisters in pack sizes of 20 and 100 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Colchicine.
Chemical names: Acetamide, N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[α]heptalen-7-yl)-(S).

Structural formula:

Molecular formula: \(\text{C}_{22}\text{H}_{25}\text{F}_{2}\text{NO}_{6}\).
Molecular mass: 399.44 g/mol
Appearance: Yellowish-white, amorphous or crystalline powder.
Solubility: Very soluble in water, rapidly recrystallising from concentrated solutions as sesquihydrate, freely soluble in ethanol (96%), practically insoluble in cyclohexane.

Colchicine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, colchicine, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, tablets containing 500 micrograms (0.5 mg) of colchicine per tablet that are bioequivalent to the reference product Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands). A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and in-vitro dissolution profiles have been provided for the proposed and originator products.
All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at a commercial-scale batch size and has shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation studies on future commercial-scale batches.

**Finished Product Specification**
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Store in the original package in order to protect from light’.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of this application from a pharmaceutical viewpoint.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Colchicine Tablets
III  NON-CLINICAL ASPECTS

III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of colchicine are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3  Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4  Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5  Ecotoxicity/environmental risk assessment (ERA)
Since Colchicine Tablets are 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.6  Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1  Introduction
The clinical pharmacology of colchicine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of colchicine.

Based on the data provided, Colchicine Tablets can be considered bioequivalent to Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands).
IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, randomised, two-period, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the applicant’s test product Colchicine Tablets (Actavis Group PTC ehf) versus the reference product, Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands), in healthy adult subjects under fasting conditions.

The subjects were administered a single dose (-500 micrograms) of either the test or the reference product with 240 ml of water after an overnight fast of at least 10 hours.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 10 days. The pharmacokinetic results are presented below:

Table: Summary of arithmetic and geometric means and 90% confidence intervals for test and reference product for colchicine.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test Product (A)</th>
<th>Reference Product (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arithmetic mean</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>$C_{max}$ (pg/mL)</td>
<td>2643.75</td>
<td>1081.45</td>
</tr>
<tr>
<td>$AUC_{0-72}$ (pg h/mL)</td>
<td>22592.63</td>
<td>6869.39</td>
</tr>
<tr>
<td>$T_{max}$ *</td>
<td>1.00 (0.50 – 2.00)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic Ln-transformed Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Geometric Mean</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>$\ln C_{max}$ (N=64)</td>
</tr>
<tr>
<td>$\ln AUC_{0-72}$ (N=61)</td>
</tr>
</tbody>
</table>

*Median (Range) has reported.

AUC$_{0-72}$ area under the plasma concentration-time curve from zero to t hours
$C_{max}$ maximum plasma concentration
$\text{t}_{max}$ time until $C_{max}$ is reached
Conclusion
In UK national Summaries of Product Characteristics (SmPC) for Colchicine Tablets, colchicine is stated to have a narrow therapeutic window and to be extremely toxic in overdose. According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), in specific cases of narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00 – 111.11%. The 90% confidence intervals of the test/reference ratio for AUC values for colchicine lie within these more stringent limits of 90.00 – 111.11%. The 90% confidence interval of the test/reference ratio for \( C_{\text{max}} \) lies within acceptable limits of 80.00% to 125.00%, also in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Colchicine tablets, 0.5 mg Tablets (TioFarma BV, Netherlands).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td>• Severe bone marrow depression</td>
<td>• Off-label use (including haemodialysis and severe renal impairment, lactose intolerance)</td>
</tr>
<tr>
<td></td>
<td>• Drug interaction with CYP 3A4 and P-glycoprotein inhibitors</td>
<td>• Overdose</td>
</tr>
<tr>
<td></td>
<td>• Myopathy and rhabdomyolysis</td>
<td>• Medication errors</td>
</tr>
<tr>
<td></td>
<td>• Use in patients with known hypersensitivity to colchicine or its excipients</td>
<td></td>
</tr>
<tr>
<td>Important potential risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing information</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Use in patients with cardiac impairment</td>
<td>• Use in patients with hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>• Use in patients with gastrointestinal disease</td>
<td>• Use in patients with renal impairment</td>
</tr>
<tr>
<td></td>
<td>• Use in patients with renal impairment</td>
<td>• Use in elderly patients (&gt; 65 years of age)</td>
</tr>
<tr>
<td></td>
<td>• Use during pregnancy and lactation</td>
<td></td>
</tr>
</tbody>
</table>
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Colchicine Tablets (Actavis Group PTC ehf) and the reference product, Colchicine tabletten, 0.5 mg Tablets (TioFarma BV, Netherlands) under fasting conditions.

The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet 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 package leaflet was English.

The results show that the package leaflet 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
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with colchicine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Annex 1 - Table of content of the PAR update for MRP and DCP
Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update section 4.2 (Posology and method of administration) of the Summary of Product Characteristics (SmPC), to improve readability.</td>
<td>UK/H/5726/001/IB/001</td>
<td>SmPC</td>
<td>13 January 2016</td>
<td>10 February 2016</td>
<td>Approval</td>
<td>Y(Annex 1.1)</td>
</tr>
</tbody>
</table>
Annex 1.1

Our Reference: PL 30306/0573 - 0003
Product: Colchicine 500microgram tablets
Marketing Authorisation Holder: Actavis Group PTC ehf
Active Ingredient(s): Colchicine.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/5726/001/IB/001

Reason:
To update section 4.2 (Posology and method of administration) of the Summary of Product Characteristics (SmPC), to improve readability.

Supporting Evidence
Revised SmPC fragment.

Evaluation
The proposed change to the SmPC is satisfactory.

Conclusion
The proposed change to SmPC and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision - Approved on 24 February 2016.