Public Assessment Report

UKPAR

Colchicine 500microgram Tablets

(colchicine)

UK Licence No: PL 20117/0262

Morningside Healthcare Limited
LAY SUMMARY

Colchicine 500microgram Tablets
(colchicine)

This is a summary of the Public Assessment Report (PAR) for Colchicine 500microgram Tablets (PL 20117/0262). It explains how the application for 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.

The product may be referred to as ‘Colchicine Tablets’ in 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?
In adults, Colchicine Tablets are used to treat gout attacks. They are also used to prevent gout flare-ups when treatment with other medicinal products is used, such as allopurinol, probenecid, and sulfipyrazone.

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-occurring 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.

In children, Colchicine Tablets may be used to treat an inherited disorder called Familial Mediterranean Fever. This leads to intermittent attacks of high temperature, pain, and other factors. Treatment for this is under specialised medical care.

Colchicine Tablets is a ‘hybrid generic medicine’. This means that Colchicine Tablets are similar to a ‘reference medicine’ already authorised in the UK called Colchicine 500 microgram Tablets (PL 29831/0055; Wockhardt Limited, UK), however unlike the reference product, Colchicine Tablets are also approved for use in children to treat an inherited disorder called Familial Mediterranean Fever.

How do Colchicine Tablets work?
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 inflamed areas. This helps to break the cycle of inflammation and reduces swelling and pain.

How are Colchicine Tablets used?
The route of administration is via the mouth (oral). Colchicine tablets should be swallowed whole with a glass of water.

The patient must always take this medicine exactly as his/her doctor has advised. The patient must check with his/her doctor or pharmacist if he/she is not sure.

The patient’s doctor will tell the patient how many tablets to take and for how long.
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 are a hybrid generic medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK). 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 are bioequivalent to the reference medicine Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK), the 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 500 microgram Tablets (Wockhardt UK Limited, UK). Therefore, the MHRA decided that, as for Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK) 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
A Marketing Authorisation was granted in the UK to Morningside Healthcare Limited on 16 June 2016.

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 July 2016.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA considered that the application for Colchicine 500 microgram Tablets (PL 20117/0262) could be approved. The product is a Prescription Only Medicine (POM) indicated for the following:

Adults
• treatment of acute gout
• prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs.

Paediatric Population:
• Colchicine is indicated in Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis.

The application for Colchicine 500 microgram Tablets was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application and cross-refers Colchicine 500 microgram Tablets (PL 29831/0055; Wockhardt UK Limited, UK), which was authorised in the UK on 23 October 2007 following a change of ownership procedure of Colchicine Tablets BP 500 micrograms (PL 04543/0096; CP Pharmaceuticals Limited). Prior to change of ownership, the reference medicinal product for this application was originally granted to Charnwood Pharmaceuticals Limited (PL 03418/5943R; Charnwood Pharmaceuticals Limited) on 17 August 1979 on the basis of a full dossier, which was subsequently reviewed in line with the acquis communitaire upon full implementation of the Medicines Act.

This application includes the indication ‘in Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis’, which although not approved in the reference product, has been previously approved in the UK for colchicine product, Colchicine Tablets BP 500mcg (PL 36301/0044; RPH Pharmaceuticals AB, Sweden).

During assessment of the application major objections were raised with respect to the efficacy and safety of the product. The application was first considered by the Committee on Human Medicines (CHM) at their meeting on 18 June 2015. The Committee provisionally concluded that further information on efficacy and safety should be requested before the product could be approved. In response to the CHM advice, the applicant provided additional data and detailed clarification of the points that had been raised. Following consideration of the applicant’s responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

The active substance, colchicine (as colchicine sesquihydrate) 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. 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 an 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.

Two bioequivalence studies were submitted to support this application, comparing the applicant’s test product Colchicine 500 microgram Tablets (Morningside Healthcare Limited) with the reference product Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK) under fasting conditions. The applicant has stated that the bioequivalence studies 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.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Colchicine Tablets outweigh the risks.

II. QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Colchicine Tablets are white to off-white coloured, circular biconvex uncoated tablets, each with “C5” embossed on one side and plain on the other side and with a diameter of 5.5 mm.

Each tablet contains 500 micrograms of the active substance, colchicine (as colchicine sesquihydrate). Other ingredients consist of the pharmaceutical excipients, lactose monohydrate, pregelatinised starch, purified talc (E553b) and stearic acid (E570).

The finished product is packed in:

1. oriented polyamide/aluminium/polyvinylchloride with aluminium lidding (OPA/Al/PVC-Alu) blisters; each blister contains 10 or 14 tablets.
2. white opaque polyvinylchloride with aluminium lidding (PVC-Alu) blisters; each blister contains 10 or 14 tablets.

Blisters of 10 tablets are available in pack sizes of 10, 20, 30, 40, 50, 60, 90 and 100 tablets.

Blisters of 14 tablets are available in pack sizes of 14, 28, 56, 84 and 112 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
Ph. Eur. Colchicine
Chemical name: (-)-N-[(7S,12aRa)-1,2,3,10-Tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide
Structural formula:

![Structural formula of Colchicine](image)

Molecular formula: C$_{22}$H$_{25}$F$_{2}$NO$_{6}$
Molecular weight: 399.44 amu
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.
Isomerism Colchicine exhibits atropisomerism. Owing to its structure, it exists as a mixture of conformers that can interconvert in solution and at ambient temperatures.
Polymorphism Colchicine exhibits polymorphism and may exist as a number of solvates, depending on isolation conditions.

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 500 microgram Tablets (Wockhardt UK Limited, UK). 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 analyses 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 provided a satisfactory declaration, confirming that lactose monohydrate from the proposed source is manufactured in compliance with the CPMP Guideline “Note for Guidance on Minimising the Risk of Transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products” and 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 this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at full-scale production batches and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. 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:
1. 30 months for OPA/Al/PVC-Alu blister packs
2. 2 years for PVC-Alu blister packs.

The special storage conditions approved for the product is “Store in the original package in order to protect from light.”

This medicinal product does not require any special temperature storage conditions.

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

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

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

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
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, 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. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of colchicine. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted two bioequivalence studies to support the application, comparing the applicant’s test product Colchicine 500 microgram tablets (Morningside Healthcare Limited, UK) with the reference product Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK) under fasting conditions.

Colchicine is categorized as a narrow therapeutic index drug. Hence in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the acceptance range for bioequivalence for colchicine is 80.00% to 125.00% for ln transformed C\textsubscript{max} and 90.00% to 111.11% for ln transformed AUC\textsubscript{0-1} values.

The first bioequivalence study submitted by the applicant was not specifically designed to demonstrate confidence intervals for a narrow therapeutic index product. This bioequivalence study was not considered relevant and will not be discussed further.

With the exception of data from the bioequivalence study detailed in Section IV.2, Pharmacokinetics below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for this application.

IV.2 Pharmacokinetics
In support of this application, the following bioequivalence study was considered:

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 500 microgram tablets (Morningside Healthcare Limited, UK) versus the reference product, Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK), in healthy adult human subjects under fasting conditions.

The subjects were administered a single dose (1 x 500 microgram tablet) 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 14 days. The pharmacokinetic results are presented below:
Table: Geometric means, ratios and 90% confidence intervals for colchicine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90% Confidence Interval for In-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>A/B</td>
</tr>
<tr>
<td>AUC₀₋₇₂</td>
<td>19496.1417</td>
<td>18934.6062</td>
<td>102.9657</td>
</tr>
<tr>
<td>Cₘₐₓ</td>
<td>2117.5163</td>
<td>2091.8384</td>
<td>101.2275</td>
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</table>

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.

Conclusion
The 90% confidence intervals of the test/reference ratio for Cₘₐₓ lie within the acceptable limits of 80.00% to 125.00%. Also, the 90% confidence intervals of the test/reference ratio for AUC₀₋₇₂ lie within the acceptance limits of 90.00% to 111.11%. Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK) under fasting conditions.

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.

The following table lists the summary of safety concerns which have been identified:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tr>
<td><strong>Important identified risks</strong></td>
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<tr>
<td>• Hypersensitivity to the active substance or to any of the excipients</td>
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<td>• Drug interaction with P-glycoprotein and cytochrome P (CYP)3A4 inhibitors</td>
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<tr>
<td>• Myopathy and rhabdomyolysis</td>
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<tr>
<td>• Use in patients with severe bone marrow depression</td>
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<tr>
<td><strong>Important potential risks</strong></td>
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<tr>
<td>• Off-label use (including haemodialysis, severe renal impairment, rare hereditary problems of galactose intolerance or glucose-galactose intolerance and Lapp lactase deficiency)</td>
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<td>• Overdose</td>
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<tr>
<td>• Medication error</td>
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<tr>
<td><strong>Missing information</strong></td>
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<tr>
<td>• Use in patients with renal impairment</td>
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<tr>
<td>• Use in elderly patients (&gt; 65 years of age)</td>
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<tr>
<td>• Risk of foetal chromosome damage during pregnancy</td>
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<tr>
<td>• Risks during breast feeding</td>
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<tr>
<td>• Use in cardiac impairment</td>
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<td><strong>Use in hepatic impairment</strong></td>
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<tr>
<td><strong>Use in gastrointestinal disease</strong></td>
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</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation activities 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 and the reference product, Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK) 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

QUALITY
The important quality characteristics of Colchicine Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of colchicine are well known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s product and the reference product Colchicine 500 microgram Tablets (Wockhardt UK Limited, UK) under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of colchicine is well known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
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 assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

**Alu-Alu blister:**
Carton for Alu-Alu blister:
PVC-Alu blister:
Carton for PVC-Alu blister:

Each tablet contains 500 micrograms of colchicine (as colchicine sesquihydrate). Contains lactose.

For oral use.

Dose: as directed by your doctor.

Keep out of the sight and reach of children.

This medicinal product does not require any special temperature storage conditions.

Store in the original package to protect from light.
Colchicine 500 microgram Tablets
(colchicine)

PL 20117/0262

**STEPS TAKEN AFTER AUTHORISATION-SUMMARY**

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