Public Assessment Report

Decentralised Procedure

Colchicine 500 microgram Tablets

(Colchicine)

Procedure No: UK/H/6003/001/DC

UK Licence Number: PL 42765/0002

Renata (UK) Limited
LAY SUMMARY

Colchicine 500 microgram Tablets

This is a summary of the Public Assessment Report (PAR) for Colchicine 500 microgram Tablets (PL 42765/0002; UK/H/6003/001/DC). It explains how Colchicine 500 microgram Tablets were 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 500 microgram Tablets.

The 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 are ‘generic medicine’. This means that Colchicine is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Colchicine Tablets BP 500 mcg (RPH Pharmaceuticals AB).

Colchicine Tablets are anti-gout medicine and contain the active ingredient colchicine which is used to treat gout in adults. This medicine is also used to prevent flare-ups of gout in adults when treatment is started with other drugs such as allopurinol, probenecid and sulfinpyrazone.

Colchicine Tablets are used in children to provide relief during attacks in Familial Mediterranean Fever.

How do Colchicine Tablets work?
Colchicine Tablets are anti-gout agents and work to prevent or treat gout attacks. Gout symptoms can develop suddenly and can involve pain in one or more joint(s). Gout is caused by too much uric acid in the blood. When uric acid levels in the blood are too high, the uric acid may form hard crystals in the joints. Colchicine Tablets work by decreasing swelling and lessening the build up of uric acid crystals that cause pain in the affected joint(s).

Colchicine Tablets provide relief from pain during attacks in Familial Mediterranean Fever by decreasing the body’s production of proteins that builds up in children with Familial Mediterranean Fever.

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

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

The recommended dose for Colchicine Tablets are:

Use in adults

Dose to treat gout attack:
The recommend dose is two Colchicine Tablets to start and followed by one Colchicine Tablets after one hour. No further tablets should then be taken for twelve 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 must 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 the treatment with Colchicine Tablets will last.

The patient’s doctor may reduce the dose of Colchicine, if the patient has kidney or liver problems. The patient will be carefully monitored for side effects. The patient should not take Colchicine Tablets, if they suffer from severe kidney or liver problems.

**Use in children and Adolescents**
In children with Familial Mediterranean Fever the recommended dose is based on age. The following daily doses may be given as a single or divided dose daily (for doses over 1mg/day):

- For children under 5 years of age the recommended dose is one tablet a day as a single dose.
- For children aged 5 years to 10 years, the usual dose is two tablets a day, as a single or divided dose.
- For children over 10 years of age, the usual dose is three tablets a day, as a single or divided dose.

The patient’s doctor may gradually adjust the dose, depending upon the reaction of the child, to a maximum of four tablets a day.

This medicine is not suitable for children who require a dose of less than one tablet a day.

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

For further information on how Colchicine is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Colchicine Tablets have been shown in studies?**
Because Colchicine Tablets are generic medicine, studies in patients have been limited to tests to determine that Colchicine is bioequivalent to the reference medicine Colchicine Tablets BP 500 mcg (RPH Pharmaceuticals AB). 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 is a generic medicine and is bioequivalent to the reference medicine Colchicine Tablets BP 500 mcg (RPH Pharmaceuticals AB), 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 were Colchicine Tablets approved?**
It was concluded that, in accordance with EU requirements, Colchicine has been shown to have comparable quality and to be bioequivalent to Colchicine Tablets BP 500 mcg (RPH Pharmaceuticals AB); the benefits are greater than the risks and recommended that Colchicine 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 (SmPCs) 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**
Ireland and the UK agreed to grant a Marketing Authorisation for Colchicine Tablets on 1 November 2017. A Marketing Authorisation was granted in the UK on 30 November 2017.

The full PAR for Colchicine follows this summary.

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

This summary was last updated in January 2018.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Renata (UK) Limited, a marketing authorisation for the medicinal product Colchicine Tablets (PL 42765/0002; UK/H/6003/001/DC). The product is a prescription-only medicine (POM).

Colchicine is indicated in adults for:
- Treatment of acute gout.
- Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs.

Colchicine is indicated in the paediatric population for:
- Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland (IE) as a Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application.

The EU reference product for this application is Colchicine Tablets BP 500 mcg which was first authorised to UCB Pharma Limited on 14 November 1979 (PL 00039/5727R), and subsequently underwent several changes of ownership procedures of which the most recent was to Recipharm Limited (PL 32446/005) authorised on 13 August 2008 and then to the current marketing authorisation holder, RPH Pharmaceuticals AB, granted on 21 November 2012 (PL 36301/0044).

Colchicine is an anti-gout medication. The mechanism of action of colchicine in the treatment of gout is not clearly understood. Colchicine is considered to act against the inflammatory response to urate crystals, by possibly inhibiting the migration of granulocytes into the inflamed area. Other properties of colchicine, such as interaction with the microtubules, could also contribute to the operation. Onset of action is approximately 12 hours after oral administration and is maximal after 1 to 2 days.

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. Familial Mediterranean Fever (FMF) is a hereditary inflammatory disorder which manifests as attacks of serositis, with the complication of amyloidosis. Daily colchicine reduces the frequency and duration of the attacks.

Two bioequivalence studies (open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence studies under fasting conditions) were submitted to support this application. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP) guidelines.

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

The RMS 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, assembly and batch release of these products.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 01 November 2017. After a subsequent national phase, a licence was granted in the UK on 30 November 2017.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 500 micrograms of colchicine as the active ingredient. Other ingredients consist of the pharmaceutical excipients:
Lactose monohydrate, maize starch, magnesium stearate and starch, pre-gelatinised

The tablets are packed in to High Density Polyethylene (HDPE) bottles with child-resistant polypropylene caps containing 100 or 500 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

II.2 Drug Substance

**INN:** Colchicine
**Eurpoean Pharmacopoeia name:** Colchicine
**Chemical name:** \((-\text{N})-(7S,12aR_\text{a})-1,2,3,10\text{-Tetramethoxy-9-oxo-5,6,7,9 tetrahydrobenzo[a]heptalen-7-yl})\text{acetamide}

**Structure:**

![Colchicine Structure](image)

**Molecular formula:** $\text{C}_{22}\text{H}_{25}\text{NO}_6$
**Molecular weight:** 399.4 amu
**Description:** Yellowish-white, amorphous or crystalline powder
**Solubility** Very soluble in water, rapidly recrystallising from concentrated solution as the 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, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product
**Pharmaceutical Development**

The development of the product has been described, the choice of excipients is justified and their functions explained.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.
All excipients comply with their respective monograph in the European Pharmacopoeia.

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.

This product does not contain or consist of genetically modified organisms (GMO).

**Manufacture of the product**
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated at full scale production batch size and has shown satisfactory results.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with the storage conditions ‘This medicinal product does not require any special temperature storage conditions. Store in the original package’ and an in-use shelf-life of 50 days when stored at or below 25 °C.

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

**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**
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
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 studies 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 Tablets BP 500 mcg (RPH Pharmaceuticals AB).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence studies:

STUDY 1
An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of the applicant’s test product Colchicine 500 microgram Tablet (Renata (UK) Limited) versus the reference product Colchicine Tablets BP 500 mcg (Recipharm Limited, UK) in healthy, adult, human subjects under fasting conditions.

The subjects were administered a single oral dose in each study period (1 x 500 microgram tablet) of either the test or the reference product under fasting conditions.

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 19 days.

Colchicine has a narrow therapeutic window and is extremely toxic in overdose. According to the CHMP bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Cort**), in specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11% The applicant sought Scientific Advice from the Medicines and Healthcare Regulatory Agency (MHRA) on this topic and was advised to follow the recommendations made in the ‘CHMP guideline on the investigation of bioequivalence’ with respect to the acceptance intervals for AUC and C\text{max} for narrow therapeutic index drugs i.e. the standard ranges for bioequivalence should be narrowed to 90-111.11%. In Europe, the C\text{max} criterion is typically narrowed where this is of importance for safety, efficacy or drug level monitoring.

The pharmacokinetic parameters were calculated from the plasma concentration versus time profile by non-compartmental model for Colchicine. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out to assess the bioequivalence between test and reference formulations. The ln-transformed pharmacokinetic parameters C\text{max}, AUC\text{0-1} and AUC\text{0-\infty} were to be...
subjected to analyses of variance (ANOVA) for Colchicine. ANOVA model was to be included Sequence, Subject (Sequence), Formulation and Period as fixed effects. Each analysis of variance was to be included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with this difference

Criteria for conclusion of bioequivalence were:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Acceptance Range of 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>80.00 – 125.00%</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{t}}$</td>
<td>90.00 – 111.11%</td>
</tr>
</tbody>
</table>

The study design is acceptable for the purpose of demonstrating bioequivalence for a narrow therapeutic drug (narrow confidence intervals for AUC).

The pharmacokinetic results are presented below:
Table: Summary of comparative bioequivalence data and 90% Confidence Interval (CI) for Colchicine

Descriptive Statistics of Formulation Means for Colchicine

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-T</td>
</tr>
<tr>
<td></td>
<td>Cmax (pg/mL)</td>
</tr>
<tr>
<td></td>
<td>AUC_0-72 (pg.h/mL)</td>
</tr>
<tr>
<td></td>
<td>t_max (h)</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from zero to t hours
AUC<sub>0-inf</sub> area under the plasma concentration-time curve from zero to inf hours
C<sub>max</sub> maximum plasma concentration

Relative Bioavailability Results for Colchicine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Means</th>
<th>90% Confidence Interval</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-T</td>
<td>Reference Product-R</td>
<td>Ratio (T/R)%</td>
</tr>
<tr>
<td>lnC&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2336.386</td>
<td>2155.114</td>
<td>108.4</td>
</tr>
<tr>
<td>lnAUC&lt;sub&gt;0-72&lt;/sub&gt;</td>
<td>21850.396</td>
<td>20729.373</td>
<td>105.4</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence interval for the ratio of geometric least-squares means was 97.61 - 120.41% for C<sub>max</sub> and the 90% confidence interval for the ratio of geometric least-squares means was 98.41 - 112.90% for AUC<sub>0-72</sub>. The 90% confidence intervals for AUC and C<sub>max</sub> lie within the acceptance acceptable limits of 80.00% to 125.00%, as per the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**’) on the investigation of bioequivalence (predefined acceptance range of 80% to 125%), but not within the narrow therapeutic index recommendation for AUC. Therefore the bioequivalence study failed the pre-specified narrow criteria for AUC.

The applicant performed a second bioequivalence study taking into consideration the findings of study 1.

In order to demonstrate equivalence according to narrow therapeutic interval criteria the applicant submitted a new study with increased sample size to obtain the required power for the AUC parameter (Study 2).

STUDY 2
An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of the applicant’s test product Colchicine 500 microgram Tablet (Renata (UK) Limited) versus the reference product Colchicine Tablets BP 500 mcg (RPH Pharmaceuticals AB) in healthy, adult, human subjects under fasting conditions.

The subjects were administered a single oral dose in each study period (1 x 500 microgram tablet) of either the test or the reference product with 240 mL of water after fasting for at least 10 hours.
Colchicine has a narrow therapeutic window and is extremely toxic in overdose. According to the CHMP bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), in specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. The applicant sought Scientific Advice from the Medicines and Healthcare Regulatory Agency (MHRA) on this topic and was advised to follow the recommendations made in the ‘CHMP guideline on the investigation of bioequivalence’ with respect to the acceptance intervals for AUC and C\textsubscript{max} for narrow therapeutic index drugs i.e. the standard ranges for bioequivalence should be narrowed to 90-111.11%. In Europe, the C\textsubscript{max} criterion is typically narrowed where this is of importance for safety, efficacy or drug level monitoring.

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 15 days.

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile by non-compartmental model for Colchicine. Statistical comparison of the pharmacokinetic parameters of the two formulations (test versus reference) was carried out to assess the bioequivalence between test and reference formulations. The ln-transformed pharmacokinetic parameters C\textsubscript{max}, AUC\textsubscript{0-t} and AUC\textsubscript{0-\infty} were to be subjected to analyses of variance (ANOVA) for Colchicine. ANOVA model was to be included Sequence, Subject (Sequence), Formulation and Period as fixed effects. Each analysis of variance was to be included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with this difference.

Criteria for conclusion of bioequivalence were:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Acceptance Range of 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{max}</td>
<td>80.00 – 125.00%</td>
</tr>
<tr>
<td>AUC\textsubscript{0-t}</td>
<td>90.00 – 111.11%</td>
</tr>
</tbody>
</table>

The study design is acceptable for the purpose of demonstrating bioequivalence for a narrow therapeutic drug (narrow confidence intervals for AUC).

Table: Summary of comparative bioequivalence data and 90% Confidence Interval (CI) for Colchicine

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD (untransformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-T</td>
</tr>
<tr>
<td>C\textsubscript{max} (pg/mL)</td>
<td>2593.854 ± 1039.1204</td>
</tr>
<tr>
<td>AUC\textsubscript{0-t} (pg.h/mL)</td>
<td>21471.713 ± 5905.1314</td>
</tr>
<tr>
<td>AUC\textsubscript{0-\infty} (pg.h/mL)</td>
<td>24896.817 ± 7175.3700</td>
</tr>
<tr>
<td>\lambda\textsubscript{d} (1/h)</td>
<td>0.023 ± 0.0032</td>
</tr>
<tr>
<td>t\textsubscript{1/2} (h)</td>
<td>31.264 ± 4.4811</td>
</tr>
<tr>
<td>AUC_%Extrap_obs (%)</td>
<td>13.396 ± 2.9492</td>
</tr>
</tbody>
</table>
AUC<sub>0-t</sub> area under the plasma concentration-time curve from zero to t hours
AUC<sub>0-inf</sub> area under the plasma concentration-time curve from zero to inf hours
C<sub>max</sub> maximum plasma concentration

### Relative Bioavailability Results for Colchicine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Means</th>
<th>90% Confidence Interval</th>
<th>Intra Subject CV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnC&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2396.770</td>
<td>2553.503</td>
<td>93.9</td>
<td>87.09 - 101.16</td>
</tr>
<tr>
<td>lnAUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>20666.908</td>
<td>21554.936</td>
<td>95.9</td>
<td>91.91 - 100.02</td>
</tr>
<tr>
<td>lnAUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>23878.247</td>
<td>24883.567</td>
<td>96.0</td>
<td>92.01 - 100.08</td>
</tr>
</tbody>
</table>

### Conclusion

The 90% confidence intervals for C<sub>max</sub> were 87.09-101.16 and for AUC<sub>0-72</sub> were 91.92-100.02.

The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for colchicine lie within the acceptable limits of 80.00% to 125.00% and for AUC fall within the narrow therapeutic index recommendation (90.00-111.11%), 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 BP 500 mcg (RPH Pharmaceuticals AB).

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety

No new safety data were submitted and none are required.

### 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.

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>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity to the active substance or any of the excipients</td>
</tr>
<tr>
<td>Myopathy and rhabdomyolysis</td>
</tr>
<tr>
<td>Severe bone marrow suppression</td>
</tr>
<tr>
<td>Serious hepatic disorders</td>
</tr>
<tr>
<td>Serious renal impairment (creatinine clearance &lt; 10mL/min)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in the elderly (&gt;65 yrs)</td>
</tr>
<tr>
<td>Concomitant use with inhibitors of CYP3A4 and P-glycoprotein may lead to colchicine toxicity</td>
</tr>
<tr>
<td>Use in patients with renal impairment.</td>
</tr>
<tr>
<td>Off-label use (including haemodialysis and severe renal impairment, lactose intolerance).</td>
</tr>
<tr>
<td>Overdose</td>
</tr>
<tr>
<td>Medication errors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use during pregnancy and lactation</td>
</tr>
<tr>
<td>Use in patients with cardiac impairment</td>
</tr>
<tr>
<td>Use in patients with hepatic impairment</td>
</tr>
<tr>
<td>Use in patients with gastrointestinal disease</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

**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 products 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.
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 MAH has submitted the following approved label texts for this medicine which is presented below:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Colchicine 500 microgram Tablets
Colchicine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 micrograms colchicine

3. LIST OF EXCIPIENTS

Contains lactose. See enclosed leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

100 Tablets
500 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Store at or below 25°C after first opening the bottle and use within 50 days.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special temperature storage conditions.
Store in the original package.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder
Renata (UK) Limited
Greenway Business Centre,
Harlow Business Park, Harlow,
CM19 5QE
United Kingdom

Distributed by
Flynn Pharma Limited
Hertlands House, Primett Road,
Stevenage, Hertfordshire,
SG1 3EE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 42765/0002
PA 2091/002/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Colchicine 500 microgram Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

<Not applicable.>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

HDPE container

1. NAME OF THE MEDICINAL PRODUCT

Colchicine 500 microgram Tablets
Colchicine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 micrograms colchicine

3. LIST OF EXCIPIENTS

Contains lactose. See enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

100 Tablets
500 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Store at or below 25°C after first opening the bottle and use within 50 days.
Open date:

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special temperature storage conditions.
Store in the original package.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Renata (UK) Limited
Greenway Business Centre,
Harlow Business Park,
Harlow
CM19 5QE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 42765/0002
PA 2091/002/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Colchicine 500 microgram Tablets
The own label supplier (Flynn Pharma Limited) has submitted the approved mock-up labelling for this medicine which is presented below:
Annex 1

Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<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 Y/N (version)</th>
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