

RISK MANAGEMENT PLAN

**“Colchicine AGEPHA
Pharma 0.5 mg tablets”**

EU Risk Management Plan for “Colchicine AGEPHA Pharma 0.5 mg tablets” (Colchicine)

RMP version to be assessed as part of this application:

RMP Version number: 0.4

Data lock point for this RMP: 03/03/2026

Date of final sign off: 25/04/2026

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP: All sections of this RMP have been updated to be in line with the latest EU format of the risk management plan (RMP). Except for these changes, there are no other significant changes in any section of this RMP.

QPPV name: Erna Lujinovic

QPPV signature: The content of this RMP has been reviewed and approved by the AGEPHA Pharma’s QPPV. The electronic signature is available on file.

Part I. Product overview

Active ingredient(s) (INN):	Colchicine
Pharmacotherapeutic group(s) (ATC Code)	Colchicine indicated for the reduction of atherothrombotic events (M04AC01)
Marketing Authorisation Holder / Applicant	Agepha Pharma s.r.o
Medicinal products to which this RMP annex refers	1
Invented name(s) in the European Economic Area (EEA)	Colchicine AGEPHA Pharma 0.5 mg tablets
Brief description of the product	<u>Chemical class</u> Colchicine AGEPHA Pharma contains Colchicine, which is isolated from the roots of the <i>Colchicum Autumnale</i> plant. Colchicine is considered a proto-alkaloid or biological amine with anti-inflammatory properties.
	<u>Summary of mode of action</u> The mechanism of action of colchicine in the prevention of major cardiovascular events is not understood. However, it is known that colchicine disrupts cytoskeletal functions through inhibition of β-tubulin polymerization into microtubules and consequently prevents the activation, degranulation, and migration of neutrophils. Evidence suggests that Colchicine may also interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1β. These anti-inflammatory effects are consistent with clinical data demonstrating that colchicine reduces high sensitivity C-reactive protein (hs-CRP).
	<u>Important information about its composition</u> Colchicine AGEPHA Pharma tablets supplied for oral administration are white to slightly yellow, round, biconvex tablet debossed with 'L1' on one side and plain on the other side containing (approx. 6.0 mm in diameter and approx. 3.1 mm in thickness) 0.5 mg of colchicine as the active ingredient and the following inactive ingredients: Gelatin, Lactose monohydrate, Magnesium stearate, Potato starch, and Talc.

Hyperlink to the Product Information	SmPC – Colchicine AGEPHA Pharma 0.5 mg tablets
Indication(s) in the EEA	Current: Colchicine AGEPHA Pharma is indicated for secondary prevention of atherothrombotic events in adult patients with coronary disease stable for at least 6 months.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: Adult: The recommended dosage of Colchicine AGEPHA Pharma for adults is 0.5 mg once a day. The maximum daily dose is 0.5 mg. Children: The safety and effectiveness of colchicine in the paediatric population has not been established yet. There is no available data. Use in the elderly (≥ 65 years): The recommended dosage of Colchicine AGEPHA Pharma in elderly (>65 years) is 0.5 mg once daily. For very elderly patients (≥75 years), colchicine should be used with caution. Patients with renal impairment: In patients with mild renal impairment, the dose is 0.5 mg per day and should be carefully monitored for adverse effects of colchicine. Colchicine is contraindicated in patients with moderate to severe renal impairment Patients with hepatic impairment: In patients with hepatic impairment, the dose is 0.5 mg per day and should be carefully monitored for side effects of colchicine. Colchicine is contraindicated in patients with severe hepatic impairment.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: Pharmaceutical form: Tablets Strength: Each tablet contains 0.5 mg of colchicine Excipients: Gelatin, Lactose monohydrate, Magnesium stearate, Potato starch, and Talc.

	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

1. Indication

Colchicine AGEPHA Pharma is indicated for secondary prevention of atherothrombotic events in adult patients with coronary disease stable for at least 6 months.

2. Brand names of concerned products (with this indication)

Colchicine AGEPHA Pharma 0.5 mg Tablets

3. Epidemiology of the disease

Incidence and prevalence: Cardiovascular disease (CVD) is leading cause of morbidity and mortality worldwide. Over the past two decades, inflammation has been identified as an additional pathway for the initiation, progression and complication of CVD. Inflammation has been shown to have a pathologic role in atherosclerosis progression, plaque destabilization and rupture, and as a response to cardiomyocyte death after myocardial infarction (MI). More than 50% of cardiovascular events occurs due to inflammation. (Ref: *Alfaddagh et al., 2020*) The increased levels of IL6 and CRP during the progression of atherosclerotic plaque gave significant evidence to correlate the incidence of future cardiovascular events in atherosclerotic patients. (Ref: *Su JH et al., 2021*) Further, elevated levels of the inflammatory biomarker high sensitivity C-reactive protein (hsCRP) have shown to be associated with an increased relative risk of coronary heart disease (37%), ischemic stroke (27%) and vascular mortality (55%).

The European Society of Cardiology (ESC) reports that there are more than 6 million new cases of CVD in the EU and over 11 million in Europe every year. CVD causes 3.9 million deaths in Europe and over 1.8 million deaths in the European Union annually, accounting for 45% of all deaths in Europe and 37% in the EU. (Ref: *Fact sheets for press, 2019*)

Demographics of the target population – age, sex, race/ethnic origin:

The occurrence of Cardiovascular disease (CVD) generally found in adult patients of age more than 35 years irrespective of sex, race / ethnic origin.

Risk factors for the disease:

General risk factors associated with CVDs are obesity, hypercholesterolemia, hypertension, diabetes, unhealthy diet, physical inactivity, and tobacco use etc.

Main treatment options:

Beta-blockers, Statins, Antiplatelets, NSAIDs and Anticoagulant, Angiotensin-converting enzyme inhibitors, Calcium channel blockers etc.

Mortality and morbidity (natural history):

In Europe, CVD causes around 3.9 million deaths annually and is responsible for 45% of all deaths. **(Ref: Fact sheets for press, 2019)**

Common morbidities are diabetes, Hypertension, and obesity etc.

4. Concomitant medication(s) in the target population:

Beta-blockers, Statins, Antiplatelets, NSAIDs and Anticoagulant, Angiotensin-converting enzyme inhibitors, Calcium channel blockers etc.

5. Important co-morbidities found in the target population:

Often, Hypertension and obesity.

Part II: Module SII - Non-clinical part of the safety specification

The applicant has not conducted any nonclinical study, instead has relied on the agency's findings of reference medicinal product - Colchicine Tiofarma 0.5 mg, tablets, USFDA listed Colcrys tablets 0.6 mg and other supporting published literature. based on the available data in published literature and reference products non-clinical part of the safety specification is discussed below.

Toxicity:

Colchicine toxicity is dose dependent. Therapeutic oral doses, including adjusted doses for patients with renal or hepatic impairment, are generally well tolerated. In animal studies, lethal doses vary by species, rats showing an LD₅₀ of 6.1 mg/kg (i.p.) and cats has LD₅₀ of 0.25 mg/kg. Clinically lethal effects in animals may take several hours to manifest. Dose-related liver, kidney & muscle toxicity observed. Newborn and female rats demonstrate higher sensitivity due to slower drug clearance. Elevated liver enzymes were seen after intraperitoneal colchicine in mice.

Colchicine was not mutagenic in the bacteria reverse mutagenicity assay (AMES test) of Salmonella typhimurium strains and Escherichia coli strain. There were no adequate studies of colchicine's carcinogenicity potential. Due to the long history of clinical experience and age of the patient population, colchicine has been considered safe in the carcinogenicity aspect. **(Ref: SBOA-Colcrys-NDA 22-352, FDA 2008)**

The nonclinical literature indicates that colchicine has detrimental effects on reproduction and development due to its inhibition of microtubule formation and cell division. The effects are species and dose-dependent, with the timing of exposure also critical for the effects on embryonic development.

Safety pharmacology:

Colchicine is a safe drug when used according to established therapeutic guidelines but causes serious systemic effects if ingested in doses that exceeded the recommendations. Following table demonstrates the safety effects observed in animals according to the organ system.

Organ system	Safety effects
Nervous system	Neurotoxic effects, seizures, myopathies and Neuropathic effects with alterations in skeletal muscle and peripheral neuropathy.
Cardiovascular system	Increase in the interstitial space, increase in myocardial stiffness and impaired myocardial contractility.
Renal system	Increase in plasma renin, decreased urine volume weight loss and dehydration.
Gastrointestinal system	Abdominal cramping, abdominal pain, diarrhea, lactose intolerance, nausea, vomiting, and elevated serum enzymes AST, elevated ALT.
Metabolism and Endocrine system	Reversible increase in the insulin secretion, increase in serum glucose and increase in serum triglycerides. Along with long-lasting increases in serum and adrenal corticosteroids
Hematopoietic system	Reduced thrombin-induced platelet aggregation and ATP secretion.

Other toxicity-related information or data:

Not applicable

Part II: Module SIII - - Clinical trial exposure

The applicant has not conducted any clinical studies of their own, rather relied on *LoDoCo* and *LoDoCo2* clinical studies, evaluating the use of low-dose colchicine tablets 0.5 mg in the treatment of chronic coronary disease and reducing the further risk factors, in conjunction with other published supporting clinical studies. Along with these 2 major studies the applicant has also referred to the supporting clinical trial - CLEAR SYNERGY.

LoDoCo (Low Dose Colchicine) was the first trial to demonstrate the proof of concept that an anti-inflammatory drug could prevent cardiovascular events in patients with CAD.

LoDoCo2 trial provides strong evidence to support repurposing of Colchicine for routine secondary prevention in patients with chronic coronary diseases.

The *LoDoCo* and *LoDoCo2* trials revealed that long term use of low dose colchicine was effective in secondary prevention in patients with coronary artery disease when used along with standard therapy like statins, antiplatelet drugs like aspirin, betablockers and other interventional methods (***Ref: Nidorf et. al., 2020; Nidorf et. al., 2013***).

The CLEAR SYNERGY trial is an important and recent large-scale randomised controlled trial evaluating the effect of low-dose colchicine in patients following acute myocardial infarction (***Ref: Jolly et al., 2025***).

Table: Summary of clinical studies LoDoCo, LoDoCo2 & CLEAR SYERGY

Acronym and name	Study design	Study population	Sample size/ subjects by arm	Study objective	Study and control drugs (dose, route, regimen)	Median follow-up	Primary Outcome
LoCoDo: Low-dose Colchicine for Secondary Prevention of Cardiovascular Disease	Prospective, randomized, observer-blinded endpoint (PROBE) trial, phase III	Stable CAD (Coronary artery disease) patients	532 282 - Colchicine group and 250 - Placebo group	To determine whether Colchicine 0.5 mg/day can reduce the risk of cardiovascular events in patients with clinically stable coronary disease.	Colchicine 0.5 mg orally daily once with standard therapy	3 years	Composite of acute coronary syndrome, fatal or nonfatal out-of-hospital cardiac arrest, non-cardioembolic ischemic stroke
LoDoCo2: Colchicine in Patients with Chronic Coronary Disease	Randomized, controlled, double-blind trial, phase III	Stable CAD (Coronary artery disease) patients	5522 2762- Colchicine group and 2760 - Placebo group	To evaluate clinical efficacy of treatment with colchicine 0.5 mg once daily as compared to placebo in patients with stable coronary artery disease on the incidence of first occurrence of the composite of cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization.	Colchicine 0.5 mg orally daily once along with standard therapy	28.6 months	Composite of Cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization

CLEAR SYNERGY (OASIS-9)	Multicentre, randomized, double-blind, placebo-controlled, 2×2 factorial trial	Patients with acute myocardial infarction (STEMI/NSTEMI) undergoing PCI	Total: 7062 patients; Colchicine: 3528; Placebo: 3534	To evaluate efficacy and safety of colchicine in reducing cardiovascular events post-MI	Colchicine 0.5 mg orally once daily (initial weight-based dosing in early phase) vs placebo	Median ~3 years (≈ 2.98 years)	Composite of cardiovascular death, myocardial infarction, stroke, or ischemia-driven coronary revascularization
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	COLCHICINE AGEPHA PHARMA 0.5 mg tablets
	Section 1.8.2: Risk Management Plan (RMP)

Following table demonstrates the overall exposure of colchicine to the patients in LoDoCo, LoDoCo2 & CLEAR SYNERGY trials.

Table SIII.1: Overall exposure in Clinical Trials

Parameter	Description of Exposure Cumulative/Pooled data
Indication	Cardiovascular disease (chronic/stable CAD + post-MI)
Duration of exposure (Median duration of follow-up)	~2.5–3 years
Number of randomized colchicine-treated patients	6572 patients
Patient-Years (Person time)	~16,500–17,000 patient-years (approx.)
Dose	Colchicine 0.5 mg orally daily once with standard therapy
Age group & sex	Adults only Mean age ~60–65 years; Female ~20%
Age group & Sex Patient year	Not explicitly reported

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programmes

The exclusion criteria applied in LoDoCo, LoDoCo2 & CLEAR SYNERGY were primarily based on established safety concerns related to colchicine pharmacokinetics, drug–drug interactions, and toxicity risks in vulnerable populations. These exclusions ensured the protection of participants and the reliability of the efficacy and safety data.

Exclusion criteria in LoDoCo Trial (2013)

1. Patients without angiographically documented coronary artery disease.
2. Patients younger than 35 years or older than 85 years.
3. Patients not clinically stable for ≥ 6 months, including those with: Recent acute coronary syndrome, Recent PCI or CABG, Unstable angina
4. Patients with major competing comorbidities that may interfere with safety or study assessments, such as: Significant renal or hepatic impairment, Severe heart failure

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| 5. Patients with contraindications to colchicine therapy, including:
Hypersensitivity to colchicine, Concomitant strong CYP3A4 inhibitors or strong P-gp inhibitors |
| 6. Patients unwilling or unable to provide informed consent. |
| 7. Patients undergone bypass surgery within 10 years |

Exclusion criteria in LoDoCo2 Trial (2020)

The LoDoCo2 trial implemented more formalized exclusion criteria. The following patient groups were excluded:

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| 1. Women who are pregnant, breast feeding or may be considering pregnancy during the study period |
| 2. Renal impairment as evidenced by a serum creatinine >150 µmol/l or estimated glomerular filtration rate (eGFR) <50mL/min/1.73m ² |
| 3. Severe heart failure – systolic or diastolic New York Heart Association Functional classification 3 or 4 |
| 4. Moderate or severe valvular heart disease considered likely to require intervention |
| 5. Dependency or frailty or an estimated life expectancy < 5 years |
| 6. Peripheral neuritis, myositis or marked myo-sensitivity to statins |
| 7. Requirement for long term colchicine therapy for any other reason |
| 8. Current enrollment in another trial |

Key Exclusion Criteria – CLEAR SYNERGY (OASIS-9)

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| 1. Known hypersensitivity or contraindication to colchicine |
| 2. Severe renal impairment (e.g., advanced kidney disease or dialysis) |
| 3. Severe hepatic disease |
| 4. Concomitant use of strong CYP3A4 or P-glycoprotein inhibitors |
| 5. History of serious neuromuscular disorders (e.g., myopathy) or predisposition to colchicine toxicity |
| 6. Limited life expectancy due to non-cardiovascular conditions |
| 7. Patients unlikely to comply with study procedures or follow-up |

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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	Section 1.8.2: Risk Management Plan (RMP)

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes.

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	not included in the clinical development program
Population with relevant different ethnic origin	not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	not included in the clinical development program
Other	not included in the clinical development program

SIV.4 Limitations of clinical trial evidence relevant to efficacy

LoDoCo2 trial

Pre-randomisation run-in period:

LoDoCo2 included a 1-month open-label run-in period with colchicine 0.5 mg once daily before randomisation. Only patients who remained stable, had no unacceptable side effects, adhered to colchicine, and remained willing to continue were randomised. Therefore, the efficacy results are most directly applicable to patients able to tolerate colchicine at treatment initiation.

Exclusion of patients intolerant during run-in:

Of 6,528 patients entering the run-in phase, 1,006 patients (15.4%) were not randomised; the most common reason was gastrointestinal upset, reported in 437 patients. This limits generalisability to patients who experience early intolerance.

Limited applicability to patients with renal impairment and other high-risk conditions:

Patients with moderate-to-severe renal impairment, severe heart failure, severe valvular heart disease, or known side effects from colchicine were excluded. This limits direct applicability to these higher-risk groups and supports the need for Product Information restrictions and warnings.

Population limited to clinically stable CAD:

Patients were required to have been clinically stable for at least 6 months before enrolment. This supports the proposed indication but limits extrapolation to acute or recent MI populations.

Under-representation of women:

The authors identified that the percentage of women enrolled was lower than expected for the general chronic coronary disease population. This may limit generalisability by sex.

No routine inflammatory biomarker measurements:

C-reactive protein or other inflammatory markers were not routinely measured at baseline. Therefore, the trial could not evaluate whether baseline inflammatory status modified colchicine treatment effect.

Limited adverse event collection for some events:

Some safety outcomes were not collected uniformly across all participants; for example, myalgia and dysesthesia were assessed only in the Netherlands cohort. This limits precision and completeness of some adverse event estimates.

CLEAR SYNERGY trial

In CLEAR SYNERGY trial, colchicine demonstrated a neutral finding in primary composite endpoints compared with placebo. However, several limitations related to study design, conduct, and external factors were identified, which are considered to have impacted the ability of the study to demonstrate treatment effect. Key limitations include;

Impact of the COVID-19 pandemic:

The study was conducted during the COVID-19 pandemic, which may have affected patient follow-up, healthcare access, adherence to study medication, and overall study conduct, thereby potentially influencing efficacy outcomes. Variation in treatment effect estimates between pre-pandemic and pandemic periods, impacting consistency of results.

High level of non-adherence:

Approximately 25% of patients reported non-adherence to the study drug. This level of reduced compliance is likely to have diluted the treatment effect and impacted on the ability to detect efficacy.

Large simple trial design with limited site monitoring:

The study utilized a “large simple” design with minimal on-site monitoring, which may have reduced oversight of protocol adherence, consistency of endpoint assessment, and data verification.

Site concentration and variability:

A substantial proportion of patients (approximately 2,500 out of 7,062) were recruited from a limited number of sites within a single geographic region (North Macedonia), which may introduce variability in clinical practice and limit generalizability.

Lack of long-term compliance data:

The absence of robust long-term adherence data limits interpretation of sustained treatment effects.

Outcome observations:

No reduction was observed in certain endpoints (e.g. pericarditis or gout) within this study; however, these findings should be interpreted in light of the limitations described above.

Importantly, no increase in serious infections was observed, supporting consistency of the safety profile.

Overall, these limitations are considered to have significantly impacted the interpretability of the efficacy results from this study. Based on the totality of evidence from other well-conducted clinical studies, is considered effective in the treatment of chronic cardiovascular diseases and the findings of this study are not considered to alter the overall benefit-risk balance.

Part II: Module SV - Post-authorisation experience

Not applicable

SV.1 post-authorisation exposure

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable

Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks**SVII.1 Identification of safety concerns in the initial RMP submission****SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP:**

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Alopecia

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Increased creatine kinase concentrations in the blood serum can occur in concomitant medication with cyclosporine or in patients suffering from a reduced renal or hepatic function.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

No New safety concern is found during the period of this RMP.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP:

Not Applicable since this is the first RMP version.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks:

Important identified risks- None

Important potential risks- None

SVII.3.2. Presentation of the missing information

Missing information- None

Part II: Module SVIII – Summary of the safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities, including adverse reaction reporting, periodic safety update reports, and signal detection, are considered sufficient to monitor the risks of colchicine.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities ongoing or planned.

III.3 Summary table of additional pharmacovigilance activities

Not Applicable.

Part IV: Plans for post-authorisation efficacy studies.

Not Applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine risk minimisation measures

Not applicable

V.2. Additional risk minimisation measures

Not applicable

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan**Summary of risk management plan for Colchicine AGEPHA Pharma 0.5mg tablet (Colchicine)**

This is a summary of the risk management plan (RMP) for Colchicine AGEPHA Pharma 0.5 mg tablet. The RMP details important risks of Colchicine AGEPHA Pharma 0.5 mg tablet how these risks can be minimized, and how more information will be obtained about COLCHICINE AGEPHA PHARMA 0.5mg tablet risks and uncertainties (missing information).

Colchicine AGEPHA Pharma 0.5 mg tablet's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Colchicine AGEPHA Pharma 0.5 mg tablet should be used.

This summary of the RMP for Colchicine AGEPHA Pharma 0.5 mg tablet should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Colchicine AGEPHA Pharma 0.5 mg tablet 's RMP.

I. The medicine and what it is used for.

Colchicine AGEPHA Pharma is indicated for secondary prevention of atherothrombotic events in adult patients with coronary disease stable for at least 6 months.

It contains Colchicine as the active substance, and it is given by the oral route.

Further information about the evaluation of Colchicine AGEPHA Pharma's benefits can be found in Colchicine AGEPHA Pharma's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page.>

II. Risks associated with the medicine and activities to minimise or further characterise the risks.

Important risks of Colchicine AGEPHA Pharma 0.5mg tablet, together with measures to minimize such risks and the proposed studies for learning more about Colchicine AGEPHA Pharma 0.5mg tablet, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Colchicine AGEPHA Pharma 0.5mg tablet are risks that need special risk management activities to further investigate or minimise the risk so that the medicinal product can be safely administered orally.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Colchicine AGEPHA Pharma 0.5mg tablet. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan**II.C.1 Studies which are conditions of the marketing authorization:**

There are no studies which are conditions of the marketing authorization or specific obligation of Colchicine AGEPHA Pharma 0.5mg tablet.

II.C.2 Other studies in post-authorization development plan:

There are no studies required for Colchicine AGEPHA Pharma 0.5mg tablet.

Part VII: Annexes

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme: Not Applicable

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan: Not Applicable

Annex 4 - Specific adverse drug reaction follow-up forms: Not Applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV: Not Applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable): Not Applicable

Annex 7 - Other supporting data (including referenced material): Provided in following pages.

Annex 8 – Summary of changes to the risk management plan over time: Not Applicable, as this is initial RMP.

Annex 7: Other supporting data (including referenced material)**List of Literature References:**

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2. Su JH, Luo MY, Liang N, Gong SX, Chen W, Huang WQ, Tian Y, Wang AP. Interleukin-6: a novel target for cardio-cerebrovascular diseases. Frontiers in pharmacology. 2021 Aug 24;12:745061.
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4. Nidorf SM, Fiolet AT, Mosterd A, Eikelboom JW, Schut A, Opstal TS, The SH, Xu XF, Ireland MA, Lenderink T, Latchem D. Colchicine in patients with chronic coronary disease. New England journal of medicine. 2020 Nov 5;383(19):1838-47.
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7. Jolly SS, d'Entremont MA, Lee SF, Mian R, Tyrwhitt J, Kedev S, Montalescot G, Cornel JH, Stanković G, Moreno R, Storey RF. Colchicine in acute myocardial infarction. New England Journal of Medicine. 2025 Feb 13;392(7):633-42.