

Decentralised Procedure

RMS D210 Final Assessment report

OVERVIEW AND LIST OF OUTSTANDING ISSUES

**MYINFLA (ex AJUSCAD) 0,5 mg, film-coated
tablet
(colchicine)**

FR/H/0774/01/DC

**Applicant: PHARMASCIENCE
INTERNATIONAL LIMITED**

Reference Member State	France
Start of the procedure:	08/07/2022
Date of this report:	13/03/2024

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	MYINFLA (ex AJUSCAD) 0,5 mg, comprimé pelliculé
Name of the drug substance (INN name):	colchicine
Pharmaco-therapeutic group (ATC Code):	M04AC01
Pharmaceutical form(s) and strength(s):	0,5 mg, film-coated tablet
Reference Number(s) for the Decentralised Procedure	FR/H/0774/001/DC
Reference Member State:	FR
Concerned Member States:	DE
Legal basis of application:	Art 8(3) Application
Applicant (name and address)	PHARMASCIENCE INTERNATIONAL LIMITED Lampousis 1 1095 Nicosia Cyprus
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Names and addresses of all ASMF holders (if different from manufacturer of active substance)	N/A
Names and addresses of all CEP holders (if different from manufacturer of active substance)	Solara Active Pharma Sciences Limited Batra Centre N° 28, Sardar Patel Road Guindy, Chennai – 600 032 - India
Names and addresses of contract companies used for clinical trials (CRO(s))	PHARMASCIENCE INC. 6111, ROYALMOUNT AVENUE, SUITE 100 MONTREAL (QC), H4P 2T4 CANADA Bioanalytical facility Algorithme Pharma Inc. 575 Armand-Frappier Blvd

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I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Ajuscad 0.5mg film-coated tablets, in Prevention of ischemic cardiovascular events in patients with atherosclerotic coronary artery disease and recent myocardial infarction, in addition to standard therapies, is considered approvable.

II EXECUTIVE SUMMARY

II.1 Problem statement

Cardiovascular diseases (CVDs) are one of the most significant disease burdens worldwide. CVD is expected to remain the leading cause of death worldwide in the next two decades despite the widespread use of effective primary and secondary preventative strategies. CVD accounts for 31.5% of all deaths and 45% of all non-communicable disease deaths, more than twice that caused by cancer, as well as more than all communicable, maternal, neonatal, and nutritional disorders combined. Despite a decline in CVD mortality in Europe, more than 4 million people die from CVD across the continent every year, with more than 1.4 million dying prematurely, before the age of 75 years. [5.4. Townsend *et al*, 2016].

Large differences in the burden of CVD between countries in the European Region remain. Of the 3.8 million total deaths in the EU-15¹, 33% were caused by CVD (1.3 million) compared with 38% of deaths in the EU-28² countries (1.9 million) and 54% of deaths in non-EU member countries (2.1 million). In countries of the EU-15, age-standardized death rates (ASDRs) for CVD in men, calculated using the 2013 ESP (ESP13) ranged from 275.2/100,000 in men in France to 480.7/100,000 in Finland, and amongst women from 174.1/100,000 in France to 391.3/100,000 in Greece. Similarly, rates of premature mortality vary across EU countries. In the EU-15 21.1% of deaths under the age of 75 years were from CVD, with ASDRs for this age group in men ranging from 72.8/100,000 in men in France to 146.5/100,000 in Greece, and in women ranging from 26.4/100,000 women in France to 56.6/100,000 women in Greece. In the EU-28, CVD accounted for 26.0% of deaths under the age of 75 years with ASDRs from additional countries in the EU-15 ranging from 105.9/100,000 men in Malta to 467.2/100,000 men in Latvia and from 39.2/100,000 women in Cyprus to 206.5/100,000 women in Bulgaria C [5.4 Townsend *et al*, 2016].

In a European Heart Network study, CVD was estimated to cost the EU economy €210 billion a year in 2015 of which 53% (€111 billion) was due to healthcare costs, 26% (€54 billion) to productivity losses, and 21% (€45 billion) to the informal care of people with CVD, with substantial variation in the economic burden across EU countries [5.4. Timmis *et al*, 2020]. In 2017, stroke accounted for 438,000 deaths across Europe (EU-28, Iceland, Israel, Norway, and Switzerland), representing 8% of total deaths. Stroke is one of the leading causes of disability, and of elevated use of health- and social-care resources, with 8% of the €798 billion cost of brain disorders being attributable to stroke. In 2017, the total economic cost of stroke, which included the costs of primary, outpatient, emergency and hospital care, medications, social care, mortality and morbidity losses, and informal care costs in the EU-28 was €57 billion; the 4 most populous countries (France, Germany, Italy and the UK accounted for 63% of all costs [5.4. Luengo-Fernandez *et al*, 2020].

The significant human and economic costs of CVDs have led the WHO to highlight the prevention and control of CVDs as an important pillar of a global action plan for prevention and control of non-

¹ EU-15: Countries in the European Union (EU) prior to the ascension of 10 candidate countries on May 1, 2004: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom (UK).

² EU-28: The 28 countries of the EU, comprised of the 15 countries in the EU prior to the ascension of the 10 candidate countries on May 1, 2004 (see Footnote 1) and 13 additional countries which have subsequently joined the EU: Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia, Slovenia.

communicable diseases (NCDs). One of the targets in the Global NCD action plan (2013 – 2020), embracing a total cardiovascular risk approach, is that at least 50% of eligible people should receive drug therapy and counselling (including glycemic control) to prevent heart attacks and strokes [5.4 WHO, 2017].

Atherosclerosis is the most common cause of myocardial infarction (MI), stroke, and peripheral arterial disease. Atherosclerosis is characterized by deposition of lipoproteins and calcium plaques in the arterial intima resulting from the interplay of lipid metabolism imbalance, maladaptive immune response, and genetic alterations [5.4. Weber and Noels, 2011]. The accumulation of arterial plaques reduces blood flow in the heart and brain, frequently resulting in cardiovascular events such as HF, MI, and stroke. Plaque rupture accounts for 75% of acute MIs, with the highest incidence reported in men over 45 years of age. In women, the incidence of MI increases beyond age 50; with the difference in gender-related prevalence attributed to the protective effects of female sex hormones, which decline after menopause [5.4. Pahwa and Jialal, 2020]. Research has shown that inflammation appears to play an important role in the initiation, progression, and manifestations of atherosclerosis. Atherosclerotic lesions begin as an accumulation of lipid-laden cells (primarily macrophages) beneath the endothelium, and progress with the further accumulation of cells, connective-tissue elements, lipids and debris through immunological and inflammatory activation. It is now widely recognized that atherosclerosis is an inflammatory, dynamic, and complex disease involving multiple cell types, especially inflammatory cells including macrophages, lymphocytes, and neutrophils as well as endothelial cells and smooth muscle cells. It is likely that the inflammatory process is responsible for the high rate of CV events despite significant advances in the treatment of risk factors such as hypercholesterolemia and hypertension. Current pharmaceutical treatment consists of reductions in serum lipoproteins, rather than combatting deleterious effects of underlying acute and chronic inflammation. Patients are at risk of repeated atherothrombotic CV events after MI as multiple inflamed plaques often co-exist in the coronary system and current therapies for CAD, such as lipid-lowering statins, do not adequately control plaque inflammation [5.4 Nguyen *et al.*, 2019; 5.4 Fiolet *et al.*, 2019]. New understanding of the inflammatory nature of CAD, by selectively targeting the inflammatory process with novel or new uses of existing therapies, may reduce cardiovascular (CV) risk.

II.2 About the product

Colchicine is a plant alkaloid with a long therapeutic history. The compound was initially extracted from the autumn crocus (*Colchicum autumnale*) and has been used for centuries, making it one of the oldest drugs still in use worldwide [5.4 Dasgeb *et al.*, 2018].

Colchicine is an effective anti-inflammatory agent used primarily to treat Familial Mediterranean Fever (FMF) and gout, both chronic inflammatory diseases, at doses ranging from 0.6 mg to 2.4 mg/day. The long-term (i.e. lifelong) use of colchicine, at doses of 1 to 2 mg/day has been well documented to be safe and reasonably well tolerated in patients with FMF, a rare genetic disease [5.4 Kallinich *et al.*, 2007]. Chronic vascular inflammation is known to play a key-role in atherosclerosis; thus, the anti-inflammatory effects of colchicine may help to reduce the occurrence of CV events.

The beneficial effects of colchicine were suggested in two retrospective studies on long-term colchicine use and the risk of CV events in patients with gout and FMF. In a cohort of 290 patients with FMF, no increased prevalence of ischemic heart disease was found as compared to a control population with chronic inflammatory disease of other origins. The authors hypothesized that this may be the result of lifelong treatment with colchicine in the FMF population [5.4 Langevitz *et al.*, 2001]. In another cohort study of 1288 patients with gout, less MIs occurred in patients who filled out at least 1 colchicine prescription vs. the no-colchicine group (1.2% vs. 2.6%, $p=0.03$). There were also trends towards reduced all-cause mortality and lower CRP level in the colchicine group vs. those who did not take colchicine [5.4 Crittenden *et al.*, 2012].

In the past several years, considerable work has highlighted the potential of colchicine in the treatment of CVD mediated by pro-inflammatory processes. In the CORE (Colchicine for REcurrent

pericarditis; 5.4 Imazio *et al.*, 2005a), COPE (Colchicine for acute Pericarditis; 5.4 Imazio *et al.*, 2005b), and CORP (Colchicine for Recurrent Pericarditis; 5.4 Imazio *et al.*, 2011a) trials, colchicine was demonstrated to be effective for the treatment and prevention of recurrent pericarditis. The COPPS (Colchicine for the Prevention of the Post-pericardiotomy Syndrome) trial demonstrated colchicine to be safe and efficacious in the prevention of post-pericardiotomy syndrome [5.4 Imazio *et al.*, 2011b] and atrial fibrillation [5.4 Imazio *et al.*, 2011c] following cardiac surgery. Colchicine was also demonstrated to be safe and effective in the prevention of early atrial fibrillation recurrence after pulmonary vein isolation, a consequence associated with a significant decrease in inflammatory mediators IL-6 and CRP [5.4 Deftereos *et al.*, 2012]. A recent systematic review and meta-analysis of randomized, controlled trials [5.4 Verma *et al.*, 2015] concluded that in a wide range of patients with established CV disease, colchicine reduces the composite rate of adverse CV outcomes.

In recent years, low-dose colchicine has been evaluated for its effect on CV events in patients with CAD. Results of the LoDoCo (Low-Dose Colchicine) [5.4 Nidorf *et al.*, 2013] trial suggested that long term low-dose administration of colchicine (0.5 mg/day) may significantly decrease the risk of CV complications in patients with stable coronary disease. This finding was confirmed with the recently published results of the large scale, randomized, placebo controlled pivotal LoDoCo2 trial in 5522 patients with chronic coronary disease [5.4 Nidorf *et al.*, 2020].

AJUSCAD Colchicine 0.5 mg Film-Coated Tablet was evaluated in the large scale, pivotal, randomized, placebo-controlled Phase III trial COLCOT (MHIPS-003) in 4745 patients with recent MI [5.4 Tardif *et al.*, 2019]. Both the active and placebo tablets were supplied by Pharmascience Inc. This landmark trial, conducted by the Montreal Heart Institute (MHI), confirmed that long-term treatment with low-dose colchicine (0.5 mg daily), in addition to standard of care, was beneficial in significantly lowering the risk of major CV events in patients who experienced a recent MI. This effect was especially pronounced in patients who had initiated colchicine treatment within 3 days after their index MI.

The current ATC code for colchicine is M04AC01 under *Antigout Preparations*. Following a formal request for classification of colchicine in AJUSCAD, the WHO determined that colchicine indicated for the reduction of atherothrombotic events would also be classified under M04AC01.

In the EU, colchicine is currently marketed in several Member States as tablets of either 0.5 mg or 1 mg in strength. In France, colchicine, as 1 mg tablets, was first marketed in 1995 and is currently approved for use for the prevention (prophylaxis) and treatment of acute gout; acute attacks of chondrocalcinosis and hydroxyapatite rheumatism, FMF, Behçet's disease, and the treatment of acute idiopathic pericarditis in combination with conventional anti-inflammatory agents (NSAIDs or corticosteroids) in patients with a primary episode of pericarditis or recurrence (with abnormal CRP), excluding post-operative surgical pericarditis, at doses ranging from 0.5 mg to 3 mg daily depending on the indication [5.4 Colchicine opocalcium 1 mg SPC, 2022]. In the US, the Reference Listed Drug (RLD) is Colcris (0.6 mg colchicine), also approved for the prophylaxis and treatment of gout flares in adults and FMF. Other FDA-approved colchicine formulations include 0.6 mg capsules (Mitigare) and a 0.6 mg/5 mL oral solution (Gloperba) for prophylaxis of gout flares in adults.

Pharmascience International Ltd. is filing an Article 8(3) Full-Mixed Market Authorization Application (MAA) for AJUSCAD (Colchicine 0.5 mg Film-Coated Tablets), a new strength of colchicine to be used in a new indication:

- Prevention of ischemic cardiovascular events in patients with atherosclerotic coronary artery disease and recent myocardial infarction, in addition to standard therapies.

The recommended dose is 0.5 mg (1 tablet) once daily.

A risk management plan is provided in [Section 1.8.2](#).

II.3 General comments on the submitted dossier

Pharmascience International Ltd. is filing an Article 8(3) Full-Mixed Market Authorization Application (MAA) for AJUSCAD (Colchicine 0.5 mg Film-Coated Tablets), a new strength of colchicine to be used in a new indication:

- Prevention of ischemic cardiovascular events in patients with atherosclerotic coronary artery disease and recent myocardial infarction, in addition to standard therapies.

The efficacy of colchicine in the proposed indication is supported by the pivotal Phase 3 clinical trial (MHIPS 003/COLCOT) [5.3.5.1 COLCOT CSR; 5.4 Tardif et al., 2019], and supportive published trials such as LoDoCo, LoDoCo2, COPS [5.4 Nidorf et al., 2013; 5.4 Nidorf et al., 2020; 5.4 Tong et al., 2020], and meta-analyses from published literature [5.4 Samuel et al., 2020; 5.4 Xia et al., 2020].

Pharmacokinetic data on AJUSCAD to support this new strength are derived from two studies sponsored by Pharmascience Inc. These are a food effect study (PMS-P5-806) and a comparative bioavailability study (PMS-P2-283) which serves as a bridging study to the Australian reference product (Colgout 0.5 mg colchicine tablets) used in the LoDoCo trial, as well as the LoDoCo2 trial.

A pre-submission meeting was held with the Agence nationale de sécurité du médicament et des produits de santé (ANSM) in July 2021 to present the clinical efficacy and safety data from the pivotal COLCOT trial and supporting bioavailability trials (Section 2.7.1).

The applicant followed this Scientific Advice.

Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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.

Regarding the manufacturing site Tjoapack Netherlands B.V, the GMP certificate is mentioned to be valid until 29 May 2022. However, validity of all GMP certificates is extended until 31.12.2022 due to COVID-19 pandemic situation.

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 pivotal study COLCOT was performed in compliance with ICH Good Clinical Practice (GCP).

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance colchicine is described in the European Pharmacopoeia. The Applicant proposes one manufacturer, for which the documentation is supported by a valid CEP.

The updated QP provided at D106 is now satisfactory, dates of audit are not exceeding 3 years.

Overall enclosed data for the active substance are found to be satisfactory. Issues concerning the particle size determination limit and the microbial quality have been resolved.

Drug Product

The drug product is a film-coated tablet containing 0.5 mg of colchicine, blue-green, with translucent to white finish, round, biconvex coated tablets, debossed with "P" on one side and "05" on the other side. The product is marketed in a multi-dose container (HDPE bottles with plastic cap and absorbent molecular sieve as desiccant).

The active substance is a BCS class 3. Particle size parameter has been identified as potentially critical on content uniformity during mixing steps and dissolution rates (the active substance concentration in the core tablet is 0.417%). The applicant has changed the colchicine supplier from India Glycol (clinical batches) to Solara. The new source Solara has been validated during the development.

The applicant has developed a new 0.5mg tablet strength using the core formulation of a 0.6mg tablet strength currently registered in Canada.

The core is film-coated: a first layer is for aesthetic purpose.

The second layer contains Eudragit RL30D at a level of 2mg per tablet. No rationale to use this excipient traditionally used in prolonged release formulations is presented. The only explanation is that the applicant initially wanted to differentiate the currently registered formulation 0.6mg immediate release formulation to the new 0.5mg formulation. No specific target for the dissolution profile was intended. It is noted that the quantity used is low (1.715%) and the impact on the in vitro release is moderate (NLT 80% in 90min). When considering the in-vivo results, this excipient has no impact on the pharmacokinetic parameters and the in-vivo release profile can be considered as an immediate release profile. Consequently the applicant's proposal that Colchicine film-coated tablet 0.5 mg can be considered an IR formulation despite the presence of the Eudragit RL30D coating, is accepted.

The choice of dissolution method is explained. A 3-tier dissolution testing for the QC method in the drug product specifications is proposed (5-25% within 15 minutes, 30-55% within 30 minutes, and $\geq 80\%$ within 90 minutes). The dissolution specifications are set according to obtained results and insure discrimination of batches with Eudragit coating weight changes.

The manufacturing process development is focused on the compression and film-coating steps. The low % of active substance in the formulation is critical at the compression step for assay and content uniformity. The eudragit coating step is critical as it can affect the appearance and the dissolution rate of the tablets. The operating parameters are validated.

A comparative bioequivalence study is submitted in order to create a bridge between the product and the Australian 0.5 mg reference product (Colgout) used in one of the supportive studies (LoDoCo) for the new cardiovascular indication. Bioequivalence is demonstrated in vivo (see Clinical assessment report). From the in-vivo results the applicant justifies that Colchicine film-coated tablet 0.5 mg can be considered an IR formulation despite the presence of the Eudragit® coating. Comparative dissolution profiles in three physiological pH (HCl 0.1N, pH4.5 and pH6.8) are present for generic and reference product (the biobatches being no longer available, they have been replaced by recent batches). The comparative dissolution profiles confirm that the dissolution of the colchicine tablet is always slower than the Australian reference product. However it is agreed that the

differences in vitro are not representative of the in vivo behaviour considering that the bioequivalence is demonstrated and in vivo results prevail.

The batch formula for the commercial size is 700.000 tablets. The size is fully validated on 3 full-scale batches.

The operating parameters in the narrative description are in line with the development conclusions.

The excipients used are well known and commonly used in the composition of tablets. The standard reference stated for each (USP/NF, Ph. Eur. or in-house) is justified. The certificate of analysis from drug product manufacturer has been provided for each excipient.

Functionality related characteristics (FRCs) of the excipients are discussed in section P.2.1.2, information is reported in 3.2.P.4.1.

TSE/BSE certificates for the excipients are enclosed in sections 3.2.P.4 and 3.2.A.2.

The drug product specification cover appropriate parameters in line with ICH Q6A guideline and Ph. Eur. monograph for tablet. The shelf-life specification includes the same testing parameters as the release specification. In both specifications, the limits are the same.

Missing reference to Ph. Eur. general methods has been added for some tests.

The analytical procedures have been described in sufficient details.

Validation of analytical methods have been presented. The missing validation reports for water and microbial tests have been added.

Batch analysis results for 3 validation batches have been provided. The batch analysis results show that the finished products meet the specifications proposed. Results of an additional batch manufactured with another active substance batch from Solara has been submitted to confirm the batch-to-batch consistency.

The degradation impurities as stated by the applicant are in compliance with results from forced degradation stability study and in line with ICH Q3B and ICH Q6A guidelines. The revised limit for the total that excludes the contribution of the impurity A is acceptable. The updated specification is now satisfactory.

A satisfactory risk assessment summary on elemental impurities in accordance with ICH Q3D guideline. The results of elemental impurities are consistently below the control thresholds (30% of oral PDE), therefore no additional control is necessary for the drug product.

A risk assessment on potential nitrosamines impurities according to EMA/189634/2019 and EMA/428592/2019 guidance has been provided. The conclusion is that there is no risk of nitrosamine impurities in the finished drug product. The "low risk" evaluation quoted for various sources of risk according to the summary of risk assessment has been clarified.

Documentation on reference substances has been completed with data on the colchicine working standard and on impurities C and D reference standards.

Drug product is packaged in HDPE bottle with a plastic cap and adsorbent molecular sieve as desiccant. This type of packaging is well known and used for solid pharmaceutical forms.

Compliance with current EU regulations are provided. The provided information for container closure system is acceptable. Additional information is provided for the desiccant.

Due to the narrow therapeutic index and to the life-threatening toxic effects of the active substance colchicine, the applicant has confirmed the child proof bottle implementation.

The provided stability information now include 36 month long term and 6 month accelerated testing stability data on 3 commercial scale batches packaged in the intended commercial container closure system. A shelf-life of 36 months can be granted for the drug product without any special storage conditions.

Specification and results of total for impurities have been updated to be in line with those display in section 3.2.P.5.1.

III.2 Non clinical aspects

Pharmacology

Colchicine is an alkaloid with antimitotic activity. At low concentrations, colchicine binds to unpolymerized tubulin heterodimers (which form the basic subunits of microtubules) to form stable complexes that effectively arrest microtubule growth; at high concentrations, it inhibits microtubule polymerization, preventing the elongation of the microtubule polymer.

The anti-inflammatory effects of colchicine are multi-modal and mainly relate to disruption of microtubules and the downstream cellular functions of leukocytes. Colchicine may also have direct or indirect effects on the inflammasome. Colchicine is thought to inhibit the NLRP3 (NALP3) inflammasome which plays an important role in the pathogenesis of atherosclerosis.

It has recently been demonstrated colchicine reduced the uptake of cholesterol crystals (a pivotal pathological marker of atherosclerotic plaque vulnerability) in endothelial cells, alleviated cholesterol crystals-induced cell injury, and suppressed the expression of NLRP3 inflammasome-related proteins and various inflammatory factors. These data suggest that colchicine plays a crucial role in alleviating the intracellular inflammatory response and NLRP3 inflammation activation, attenuating the levels of cellular oxidative stress and pyroptosis in endothelial cells via regulating AMPK/SIRT1 signaling, which may be a concrete mechanism for the secondary prevention of atherosclerotic cardiovascular disease.

Overall, the body of published literature since the 1980's has shown that colchicine exerts cardio-protective, anti-inflammatory and anti-atherosclerotic effects in several animal models in vivo (mice, rats, dogs and rabbits).

Review proposed by MAH is deemed acceptable.

Pharmacokinetics

Information on the non-clinical pharmacokinetics of colchicine was sourced from published literature. No new pharmacokinetic studies have been performed.

Although colchicine is lipophilic, and thus readily absorbed in the jejunum and ileum, gastrointestinal absorption after oral ingestion is highly variable, ranging between 24% - 88% of the dose, since colchicine is partially blocked by the intestinal barrier. Peak-plasma concentration after a single oral dose of 1 mg occurs within 30 – 120 minutes post-ingestion. With repeated doses of about 1 mg/day, steady-state is achieved within 8 days, with concentrations ranging from 0.3 to 2.5 ng/mL.

In animal models (mice, rats, hamsters, rabbits, dogs, and sheep), colchicine distributes into multiple tissues but primarily into bile, liver, and kidney. P-glycoprotein expression limits the exposure of cells that are protected by effective physiological barriers. Therefore, the main risks related to colchicine distribution stem from P-glycoprotein saturation by concomitant medications or other causes of P-glycoprotein dysfunction. Additionally, colchicine is eliminated primarily by hepatic metabolism via CYP 3A4. Co-administration of colchicine with known inhibitors or substrates of CYP3A4 may therefore inhibit colchicine metabolism, resulting in concentration-related toxicity.

Colchicine is mainly metabolized in the liver via oxidative demethylation. In animal species, the specific cytochrome P450 isoform involved has not been identified, but in humans the metabolism is carried out by isoform CYP 3A4. The primary metabolites in all species are 2- and 3-demethyl-colchicine (2-DMC and 3-DMC).

Colchicine and its metabolites are eliminated mainly through the kidneys and bile, with gastrointestinal tract lining cell turnover playing a variable role in the colchicine elimination.

The proposed SPC included in this MAA contains warnings and precautions addressing the potential for drug interactions that are consistent with the recent approved labeling for Colcris.

Toxicology

Information on the non-clinical toxicology of colchicine was sourced from published literature. No new toxicology studies have been performed.

Data on the toxicology of colchicine come from original studies conducted in the 1950-1970's, studies that pre-date modern GLP requirements and regulatory standards. Despite the gaps in the nonclinical data, the widely known clinical experience and clinical toxicology of the drug contribute substantial information to understanding the risks of the drug.

Adverse effects are primarily detected in gastrointestinal, muscle, and some hematopoietic cells. While colchicine has been suspected to cause seizures, studies in rodents administered intra-cerebral injections of colchicine suggest that these effects are mediated by neuronal damage caused by inflammation rather than a lowering of the seizure threshold. Colchicine has been associated with muscle weakness, changes in gait and body positioning. Results from dose-ranging studies in rabbits and canines, colchicine was not associated with any demonstrable risk of cardiovascular toxicity in vitro (hERG; human ether-a-go-go-related gene) or in vivo.

The most commonly reported side effects of colchicine in a clinical setting are GI-related and include abdominal cramping, abdominal pain, lactose intolerance, nausea, vomiting, and elevated serum AST and ALT enzymes. Similar effects are observed in animal studies, with vomiting, diarrhea and blood diarrhea the most common early signs of GI effects.

Colchicine doses in excess of 0.5 mg/kg are generally considered toxic, although lower doses may cause significant side effects, illustrating its narrow therapeutic index. Overdosing of colchicine may eventually lead to multiple organ failure, including bone marrow suppression, hemolysis, liver failure, renal failure, convulsions, and cardiac arrest, and is often lethal.

Colchicine has adverse effects on sperm development (fertility), early embryonic development and implantation, organogenesis (teratology) and late-stage embryonic development. These effects are consistent with colchicine's pharmacodynamic effect as an inhibitor of microtubule formation and resulting disruptions of cytoskeletal functions, cell movement and cell division.

Environmental Risk Assessment (ERA)

In line with the CHMP Guideline, as the $PEC_{\text{SURFACE WATER}}$ for AJUSCAD, calculated in Phase I, is 0.0025 µg/mL, which is less than the threshold of concern 0.01 µg/L, Phase II testing is not required. It can therefore be assumed that AJUSCAD is unlikely to represent a risk for the environment following its prescribed usage in patients.

Assessor's comment:

*Colchicine being one of the oldest therapeutic substances known to mankind. Furthermore, the proposed total daily dose (0.5 mg) for the proposed indication in cardiovascular disease is below the prescribed daily doses of colchicine products approved worldwide for gout and FMF (0.6 – 2.4 mg). Therefore, **no objection is raised regarding the approach chosen by MAH and the non-clinical data presented for this full-mixed application.**

*MAH indeed conducted no specific non-clinical study per se, **as an up-to-date bibliographic review of colchicine pharmacological properties** was deemed sufficient. This latter was primarily based upon data found in the FDA-approved medicinal product Colcrys dossier, 2008; and data collected by CHP Pharma, 2020. Of note: the core PD properties supportive of the proposed indication in cardiovascular disease (i.e. the cardioprotective, anti-inflammatory and anti-sclerotic properties) were demonstrated in various rodent and non-rodent animal models.

*Additionally, few non-clinical data on the safety pharmacology, PK and toxicology of colchicine (extension of its pharmacologic activity) were also provided in the review (obtained from various animal models, exposed via enteral and parenteral routes; tabulated summaries and safety margins also provided). **Yet the long and widely known clinical experience is considered sufficient** enough to compensate for the lacks and gaps found in the original studies quoted, conducted decades before the current GLP requirements and regulatory standards.

*Furthermore this non-clinical review is **paralleled with cross-reference to three clinical trials that were specifically conducted to measure colchicine efficacy and safety** (at low dose regimen, i.e. 0.5-0.6 mg/day) in the very scope of cardiovascular disease treatment was deemed sufficient (see Clinical AR).

*Modules 2.4 (NC overview) and 2.6 (NC written and tabulated summaries) of the CTD thus present already available public information, **clearly summarized and/or tabulated**.

***However, labelling of sections 4.6 and 5.3 of the SmPC** should be completed (see annotated SPC).

III.3 Clinical aspects

Pharmacokinetics

To support the application, two studies have been submitted:

- A food effect study (PMS-P5-806) which provide additional data on food effect.
- A comparative bioavailability study (PMS-P2-283) which serves as a bridging study to the Australian reference product (Colgout 0.5 mg colchicine tablets) used in the LoDoCo trial, as well as the LoDoCo2 trial. The goal of these studies is to determine whether adding colchicine 0.5 mg/day to standard secondary prevention therapies including aspirin and high-dose statins reduces the risk of cardiovascular events in patients with objectively diagnosed and clinically stable coronary disease.

The table below lists the performed clinical studies:

Study Identifier (Date of Study)	Study Objective	Study Design and Type of Control	Test Product, Dosage	Treatment	Number of Subjects Mean Age (M, F)
PMS-P2-283 (2015/07/01 to 2015/07/19)	To compare the bioavailability of two different formulations of colchicine	Single center, randomized, single dose, blinded, 2- period, 2-sequence, crossover study	Test: AJUSCAD colchicine 0.5 mg film-coated tablet Reference: Colgout® (Colchicine) tablet 0.5 mg	Single oral dose administered twice, 14 days apart Fasting conditions	N = 32 35 years (M = 17, F = 15)
PMS-P5-806 (2015/07/02 to 2015/07/20)	To evaluate the effect of food on the relative bioavailability	Single center, randomized, single dose, laboratory- blinded, 2-period, 2-sequence, crossover study	AJUSCAD colchicine 0.5 mg film-coated tablet	Single oral dose administered twice, 14 days apart Fasting and fed conditions	N = 24 38 years (M = 12, F = 12)

Source: 5.3.1.2 PMS-P2-283 Clinical Study Report; PMS-P5-806 Clinical Study Report.

• Study PMS-P2-283: Bioavailability study

The study was a single center, randomized, single dose, blinded, 2-period, 2 sequence, crossover design in 32 healthy male and female subjects. After a supervised overnight fast, a single 0.5 mg oral dose of the assigned formulation was administered in the morning.

Blood samples were collected pre-dose at regular intervals up to 72.00 hours after dosing. Colchicine was measured in human plasma using a validated LC/MS/MS method.

The primary PK parameters were pre-defined as Cmax and AUC0-72h.

The 90% confidence interval for the ratio of the test and reference product fell within the acceptance range of 80.00 to 125.00% for Cmax and AUC0-72h.

• Study PMS-P5-806: Food-effect study

The study was a single center, randomized, single dose, laboratory-blinded, 2-period, 2 sequence, crossover design in 24 healthy male and female subjects. Depending on the modalities of food administration:

- for treatment 1 (fed conditions): following an overnight fast of at least 10 hours, subjects received a high-fat, high calorie breakfast 30 minutes prior to drug administration. Thirty minutes after the start of the breakfast, a single dose of the assigned formulation was administered with approximately 240 mL of water.

- for treatment 2 (fasted conditions): Subjects fasted overnight for at least 10 hours prior to drug administration. A single dose of the assigned formulation was administered with approximately 240 mL of water.

Blood samples were collected pre-dose at regular intervals up to 72.00 hours after dosing. Colchicine

was measured in human plasma using a validated LC/MS/MS method. The primary PK parameters were pre-defined as C_{max} and AUC_{0-72h}. The 90% confidence interval for the ratio of the treatment 1/ treatment 2 fell within the acceptance range of 80.00 to 125.00% for C_{max} and AUC_{0-72h}.

Conclusion

The results of PMS-P2-283 demonstrate that AJUSCAD is considered bioequivalent to the Colgout tablet used in the supportive LoDoCo and LoDoCo2 for which the goal is to determine whether adding colchicine 0.5 mg/day to standard secondary prevention therapies including aspirin and high-dose statins reduces the risk of cardiovascular events in patients with objectively diagnosed and clinically stable coronary disease.

The results of PMS-P5-806 indicated that no significant food effect was observed for AJUSCAD. Therefore, the dosing recommendation will be that AJUSCAD can be taken with or without food.

As a reminder, these two studies are only supportive and confirm a rapid absorption of AJUSCAD as expected.

No additional PK data in target population were provided. The target population is elderly with risks of renal failure or hepatic failure. Since there may be a risk of increased exposure with colchicine, and also with potential of drug-drug interactions, see discussions regarding the risk of overdose in the target population in the Safety part.

Pharmacodynamics

The current ATC code for colchicine is M04AC01 under Antigout Preparations. Following a formal request for classification of colchicine in AJUSCAD, the WHO determined that colchicine indicated for the reduction of atherothrombotic events would also be classified under M04AC01.

The primary mechanism of action of colchicine is tubulin disruption, leading to subsequent down-regulation of multiple inflammatory pathways and modulation of innate immunity.

Some more recently described mechanisms include various inhibitory effects on macrophages, the inhibition of key inflammatory signaling networks known as inflammasomes, and stimulation of dendritic cell maturation and antigen presentation.

Colchicine also has anti-fibrotic activities and various effects on endothelial function. The therapeutic use of colchicine has thus in recent years extended beyond gouty arthritis and Familial Mediterranean Fever (FMF), to osteoarthritis, pericarditis, and cardiovascular complications of atherosclerosis.

Colchicine's direct or indirect inhibition of the NLRP3 (NALP3) inflammasome may play an important role in the pathogenesis of atherosclerosis.

No new data are provided regarding this first application in a new indication in CV prevention.

Clinical efficacy

The efficacy of colchicine in the proposed indication is supported by the pivotal Phase 3 clinical trial (MHIPS 003/COLCOT), and supportive published trials such as LoDoCo, LoDoCo2, COPS al., 2020], and meta-analyses from published literature.

In the large-scale, global, multi-center, double-blind, placebo-controlled **pivotal COLCOT trial**,

- Design : there was no major methodological issues.
- Patients seemed to be well representative of the patients with CAD.

Patients have been treated in the range of 0 to 30 days post-MI according to study centres or regions: from day 0 to 3, immediately after the index event, in-hospital, or from day 4 to 7, in the early post-discharge period, or later, from day 8 to 30.

The mean delay between the index MI and randomization was 13.5 days. It was of 9 days in Europe, vs 18 days in North America. France was the country with the greater rate of patients recruited within the 0-3 days period, followed by Germany and Lebanon compared with the American countries which had a greater number of patients recruited within the 8-42 days period.

According to the ad hoc sub analysis which studied the time-to-treatment-initiation (TTI) of colchicine after myocardial infarction, results suggest that early suppression of inflammation after MI provides greater benefits, with a reduction of 48% in the risk of the composite primary endpoint when colchicine was initiated between Days 0 and 3, as compared with placebo [N=1193, HR = 0.52; 95% confidence intervals (CI): 0.32-0.84].

This sub-analysis shows a reduction of 65% for the endpoint UHARCR in the same period of TTI 0-3 days (0.35, 95% CI, 0.14-0.88, P=0.026). Unlike the other components of the primary endpoint, the stroke endpoint was similarly and importantly reduced in the early and the late subgroups (<3 and ≥8 days), respectively HR 0.21 (N=1193, 95% CI 0.02–1.81, P = 0.156) and HR 0.19 (N=2748, 95% CI 0.04–0.84, P = 0.029).

Patients with heart failure were supposed to be excluded, as well as patients with type 2 myocardial infarction, which will need to be reflected in the definition of the target population.

- Treatment: colchicine 0.5mg once daily was taken for a median duration of 19.6 months.

Patients were randomized at 13.5 ± 10.1 days following the index MI; 25.6% were in the Day 0-3 group, 15.4% were in the Day 4-7 group, and 59.0% were in the Day 8-30 group.

- Regarding the clinical efficacy endpoint:

The clinical relevance of the primary endpoint can be acknowledged. The primary composite efficacy endpoint, the components CV death, resuscitated cardiac arrest, acute MI and stroke are hard clinical events and robust components. The component Urgent Hospitalization for Angina Requiring Coronary Revascularization (UHARCR), includes only the most severe and urgent clinical events, leading to an unplanned coronary revascularization procedure. According to literature, these events were associated with a higher risk for subsequent rehospitalizations, both all-cause and cardiovascular. Furthermore, a blinded central adjudication of clinical endpoints by an independent Clinical Endpoint Committee is done, which reduces the risk of bias.

Key secondary endpoints comparing the event rate of CV death and all-cause mortality, were considered of relevance.

However, the definition of all the components have been provided.

- Results:

In this event-driven trial, the number of 301 events based on the primary endpoint was reached.

The risk of CV events (i.e. primary composite efficacy endpoint, CV death, resuscitated cardiac arrest, acute MI, stroke and UHARCR), as assessed in a time-to event analysis, was reduced by 23% in the ITT population (131 events [5.5%] vs 170 [7.1%]; HR 0.77; 95% CI, 0.61 to 0.96; P=0.02), 28% in PP population, and 35% in the on-treatment analysis, in patients randomized to AJUSCAD Colchicine 0.5 mg.

The risk reductions were due to favourable effects of colchicine on the point estimate for the hazard ratio of all components of the primary endpoint.

However, taken individually, there is some results for the main components, acute MI and CV deaths, did not demonstrate a significant difference between groups: 89 events [3.8%] in the colchicine group vs 98 in the placebo group [4.1%]; HR: 0.91; 95% CI: 0.68 to 1.11; p=0.52) for acute MI and 20 events [0.8%] in the colchicine group vs 24 in the placebo group [1.0%]; HR: 0.84; 95% CI: 0.46 to 1.52; p=0.56) for CV deaths. The Applicant recalls that results showed a trend in the right direction for all the components, even though it was not expected to have a significant effect on CV mortality. Acute MI was the most frequently reported component (3.8% colchicine vs 4.1% placebo).

In terms of statistics, the effect of colchicine on the composite endpoint is mainly drawn by the UHARCR outcome, which is also the less indicative of clinical benefit (25 of 2366 [1.1%] vs. 50 of 2379 [2.1%]; HR: 0.50; 95% CI: 0.31 to 0.81; p 0.005).

The other main differences in primary outcome components are drawn by stroke, which includes both hemorrhage or infarction origins. Even if they are very different mechanisms, they are of similar concern and both can occur in post-MI patients. The number of strokes was significantly reduced, with 5 events [0.2%] in the colchicine group vs 19 in the placebo group [0.8%]; HR: 0.26; 95% CI: 0.1 to 0.70; p=0.01).

The secondary composite endpoint (composite of cardiovascular death, cardiac arrest, acute MI or stroke) was not significantly reduced in the colchicine group. (111 events (4.7%) in the colchicine group, as compared with 130 events (5.5%) in the placebo group; HR 0.85; 95% CI, 0.66 to 1.10, p=0.22) but results showed a trend in the right direction for all the components.

Some other results do not appear favourable in the colchicine group: no decrease in overall mortality (43 deaths (1.8%) in the colchicine group, as compared with 44 deaths (1.8%) in the placebo group ; HR 0.98; 95% CI, 0.64-1.49, p=0.93), and numerically, more non-CV deaths, more DVT/PE (10 events (0.4%) in the colchicine group, as compared with 7 events (0.3%) in the placebo group ; HR 1.43; 95% CI, 0.54-3.75, p=0.47) and more hospitalizations for heart failure (25 events (1.1%) in the colchicine group, as compared with 18 events (0.8%) in the placebo group ; HR 1.39; 95% CI, 0.76-2.55, p=0.28).

These results were observed against a background of appropriate standard of care medications, which included aspirin, a second anti-platelet agent and a statin in 98 to 99% of patients. In addition, PCI was performed in 93% of patients for their index MI.

Subgroup analyses (by gender, smoking status, history of diabetes, history of hypertension, prior MI, prior PCI or CABG, prior stroke or TIA, and baseline WBC count) of the primary endpoint showed no significant heterogeneity compared to the effect on the global study population.

In post-hoc analyses, the beneficial effects of early initiation of colchicine were demonstrated for UHARCR, all coronary revascularization and the composite of CV death, RCA, MI, or stroke. According to the Applicant, in clinical practice, the obvious time to start colchicine treatment would be preferably in hospital, at the time of presentation with an acute coronary event. France was the country with the greater rate of patients recruited within the 0-3 days period, followed by Germany and Lebanon compared with the American countries which had a greater number of patients recruited within the 8-42 days period.

A prolonged duration of treatment of more than 2 years has been discussed.

Considering the limited data on efficacy and more especially the low number of events after 2 years of treatments, and the absence of significant difference between groups, the benefit of a prolonged duration of treatment is not totally demonstrated.

Overall, among patients with a recent MI, administration of AJUSCAD Colchicine 0.5 mg Film-Coated Tablet once daily led to a statistically significant lower rate of ischemic CV events compared to placebo. In the context of the procedure of an initial MA in a new indication, answers to all the concerns regarding the COLCOT study provide a better understanding in which conditions colchicine could benefit to patients.

Low-dose colchicine has also been evaluated for its effect on CV events in patients with CAD in **2 supportive studies, LODOCO and LODOCO2.**

The randomised patients were with stable coronary disease for ≤ 6 months in LODOCO and > 6 months in LODOCO2, which differ from patients at initiation of COLCOT (< 1 month after myocardial infarction). However, it is acknowledged that they correspond to the characteristics of the patients of COLCOT study around 6 months of treatment.

Therefore, results of these studies can be considered of interest mostly from a safety point of view. However, LODOCO2 study also resulted in a significant reduction of the primary endpoint (cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary

revascularization), i.e 31% lower relative risk with colchicine 0.5 mg compared to placebo (HR=0.69 ; 95% CI 0.57 - 0.83; P < 0.001), showing some consistency between studies and providing further support for the potential benefits of anti-inflammatory therapy in patients with coronary disease.

The characteristics of patients in LODOCO and LODOCO2 were well representative of the stable CAD disease. The majority of patients received standard medical care including anti-thrombotic agents (single or DAPT), lipid modifying agents, renin–angiotensin inhibitor and beta-blocking agents.

The LODOCO study is the oldest one, open-label (PROBE), small size, with methodological limitations. Therefore, efficacy results are difficult to interpret.

The LODOCO2 study was overall well conducted, randomized, double blind, placebo-controlled and of larger scale than LODOCO. There seems to be no apparent risk of bias.

LODOCO2 concluded to the efficacy of colchicine administered for a median of 28.6 months to reduce by 31% a composite primary outcome of CV death, spontaneous MI, ischemic stroke and ischemia-driven coronary revascularization (187 events (6.8%) in the colchicine group, as compared with 264 events (9.6%) in the placebo group; HR 0.69; 95% CI, 0.57 to 0.83, p<0.001).

LODOCO2 also allowed to conclude to a 28% reduction of the secondary endpoint, MACE (CV deaths, MI, stroke), with 115 events (4.2%) in the colchicine group, as compared with 157 events (5.7%) in the placebo group; HR 0.72; 95% CI, 0.57 to 0.92, p=0.007).

Lastly, in the LODOCO2 study, there were numerically more deaths from any cause (73 deaths (2.6%) in the colchicine group, as compared with 60 deaths (2.2%) in the placebo group; HR 1.21; 95% CI, 0.86 to 1.71), but no significant difference between groups on DVT/PE (17 events (0.6%) in the colchicine group, as compared with 16 events (0.6%) in the placebo group; HR 1.06; 95% CI, 0.53 to 2.10) and on CV deaths (20 deaths (0.7%) in the colchicine group, as compared with 25 deaths (0.9%) in the placebo group; HR 0.80; 95% CI, 0.44 to 1.44).

Sensitivity analyses that pooled the results of COLCOT and LoDoCo2 trials demonstrated similar effect estimates for the primary composite outcome and the component outcomes. Furthermore, the Applicant concludes that combined data from COLCOT and LoDoCo trials confirm that colchicine reduces the risk of MI, ischemic stroke, and unplanned revascularization, and demonstrate a (non-significant) trend towards a reduction in CV death.

In contrast to the LoDoCo, and LoDoCo 2 supportive studies which were conducted in stable CAD patients, **the COPS study is another supportive study** conducted with low dose colchicine in patient with ACS. This trial is relevant for the MAA since it included patients with ACS and colchicine treatment for at least 12 months, but the dose is not the one proposed for the MA (1 mg/day for month 1 and 0.5 mg after).

Colchicine therapy in the COPS study was started early, in patients who presented with ACS and had evidence of CAD. Therefore, patients of COPS study were more like those in COLCOT, but were randomised probably even earlier, i.e during hospitalisation for the index event, while patients in COLCOT could be recruited until 30 days post-MI. However, the time frame between ACS and treatment initiation was not provided.

According to the Applicant, in clinical practice, the obvious time to start colchicine treatment would be preferably in hospital, at the time of presentation with an acute coronary event.

This small trial was randomized, double blind, placebo controlled, with no major methodological issues.

However, it should be noted that the trial was stopped early due to recruitment problems, with 795 patients randomized (1009 planned).

Colchicine therapy in the COPS study was started with a higher dose during one month (0,5 mg x 2/day). Treatment duration in COPS was limited to 12 months compared to the approximately 2-year treatment durations in the COLCOT and LoDoCo2 trials.

The analysis of the primary outcome showed a non-significant reduction in primary outcome (composite of death from any cause, ACS (STEMI/non-STEMI/UA), ischemia-driven urgent

revascularization and non-cardioembolic ischemic stroke): 24 events in the colchicine group, as compared with 38 events in the placebo group ; HR 0.65 ; 95% CI 0.38-1.09, P = 0.10. Therefore, the study is inconclusive.

Furthermore, there was a numerical increase of overall mortality (8 deaths in the colchicine group, as compared with 1 deaths in the placebo group ; HR 8.20 ; 95% CI 1.03-65.61, P = 0.047), but no significant difference between groups on CV deaths (3 deaths in the colchicine group vs 1 death in the placebo group) and non-CV deaths (2 deaths on-treatment, 3 deaths in patients with early discontinuation in the colchicine group) was found.

Furthermore, in the meta-analysis conducted by Fiolet et al. (2021) on 5 clinical trials, results also showed a trend in the right direction for CV mortality. The majority of fatalities were of non-cardiovascular origin.

In a **recent systematic review and meta-analysis** on a pooled sample size of 11,594 patients, it was concluded that the addition of low-dose colchicine to standard medical therapy consistently reduced the incidence of major CV events, except CV mortality, when compared to standard medical therapy alone.

Colchicine was associated with significant 32% reduction of primary endpoint (CV death, MI, stroke, urgent revascularization as defined in each study), 38% reduction of acute MI (with high heterogeneity), 62% reduction of stroke and 54% of urgent coronary revascularization.

However, colchicine has no effect on CV mortality, nor on MACE (CV death, MI, stroke), nor atrial fibrillation.

The effect of primary outcome was consistent among subgroups, especially in patients with previous PCI or CABG.

Lastly, the Applicant informs that the use of low-dose colchicine has been endorsed by clinicians [Marquis-Gravel et al., 2021] and in clinical guidelines such as the **European Society of Cardiology (ESC) 2021 guidelines on CV disease prevention**. As per ESC, low-dose colchicine (0.5 mg o.d.) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy [Visseren et al., 2021]. This is also aligned with the **recent Health Canada approval of MYINFLA** in the “reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including LDL-C lowering and antithrombotic drug treatment”. [MYINFLA Canadian Product Monograph, 2021]. However, although supportive, this information does not exempt the European authorities to further examine all the efficacy and safety data needed to conclude to the benefit-risk ratio of this drug in the appropriate target population. The objective is to articulate this possible alternative within the existing therapies and in particular for the most target population and under the framework of a MA.

To conclude, based on the pivotal and supportive study results, submitted literature, clinical guidelines and recommendation, a clinical interest with a globally favourable benefit/risk balance could be established.

Overall, among patients with a recent MI, administration of AJUSCAD Colchicine 0.5 mg Film-Coated Tablet once daily led to a statistically significant lower rate of ischemic CV events compared to placebo. In the context of the procedure of an initial MA in a new indication, answers to all the concerns regarding the COLCOT study and the supportive studies provide a better understanding in which conditions colchicine could benefit to patients with CAD after recent myocardial infarct, and addition to lipid regulation and platelet inhibition therapies.

Clinical safety

The results presented by the MAH are consistent with the known safety profile of colchicine.

The most common adverse events reported in these studies were gastrointestinal (diarrhoea, vomiting, abdominal pain).

Regarding COLCOT study, there was no significant differences in serious treatment emergent adverse events (TEAEs) in colchicine vs placebo groups (16.4 % vs 17 %). The most frequently reported serious TEAEs were cardiac disorders (6 % vs 6.6 %), infections (2.2 % vs 1.6 %), gastro intestinal events (2 % vs 1.5 %) and neoplasms (2 % vs 1.9 %) in colchicine vs placebo groups. In colchicine group, there was no significant laboratory abnormalities. Pneumonia was reported as a serious adverse event in 0.9% of patients in the colchicine group and 0.4% in the placebo group (P=0.03). The MAH discussed in the response document that the data regarding the risk of infection especially the risk of pneumonia, are divergent between (COLCOT, LoDoCo2 and meta-analysis). Given this, the MAH will closely monitor this risk of infections and infestations and particularly pneumonia through routine pharmacovigilance and if necessary submit a safety review in the framework of the next PSUR. Less than 1 % of patients had a dose reduction (0.5 mg every 2 days) because of an AE but there was no study discontinuation in colchicine group.

Regarding LOCODO study, intestinal tolerance led to an early withdrawal of therapy (before 4 weeks) in 32 patients (11 %). Colchicine treatment was discontinued for 30 patients (12 %) after a mean period of 2.36 years. Colchicine treatment was discontinued for 30 patients (12 %) after a mean period of 2.36 years.

Regarding LOCODO2 study, an unexpected increase of 21 % of overall mortality and a marginally 51 % significant increase in non-cardiovascular deaths were observed. To be noted that myalgia was significantly increased in colchicine group. The MAH could not provide more details concerning the non-CV mortality and causality with colchicine since the on-treatment analysis show an even higher increase in non-CV mortality (HR 1.86) nor an in-depth analysis of context and risk factors that might have led to increase non-CV mortality (history of cancer, altered renal function, respiratory disease, dementia) because LoDoCo2 is a supportive reference and was not sponsored by the MAH. Thus, the MAH did not have access to the study data.

From meta-analyses, a marginally significant increase in non-CV mortality (38 %) was observed for colchicine. This aspect remain ambiguous and deserve further clarification. Colchicine was associated with non-significantly but numerically more DVT/PE, more infections and especially pneumonia, more hospitalizations for GI events. New incidence of cancer risk was not increased in colchicine treated patients compared to control/placebo. These results are consistent with SRMA by *XIA et al 2020*, who reported results on myalgia (non-significantly but numerically increased in colchicine group).

The incidence of safety outcomes did not differ between groups ($p>0.05$) and the increased power from pooled analyses provide reassurance about the safety of colchicine for the outcome of all cause mortality.

To be noted that given the data in the literature and the recommendations in the guidelines (AHA, ESC), the measures taken to reduce the risk of colchicine interacting with statins (mentioned in the product information) are considered sufficient. RMS agreed that no new safety signals emerged from the clinical studies data.

Moreover, in the previous PSUSA (EMA/PRAC/235021/2019, minutes of the PRAC meeting on 12-15 March 2019 and EMA/CMDh/304398/2019, minutes of the CMDh meeting on 26-28 March 2019), it was requested that the product information should be updated to include “hepatotoxicity” as an undesirable effect with frequency ‘not known’ in section 4.8 of the SmPC and “liver damage” in section 4 of the package leaflet. Therefore, the MAH added this effect in section 4.8 of the SmPC and section 4 of the package leaflet. Nevertheless, the MAH mentioned in section 4 of the PIL that liver damage is a rare effect, so the MAH is requested to modify the frequency from “rare” to “not known”. Moreover, the MAH should present section 4.8 with the frequencies of the adverse reactions.

Colchicine has a narrow therapeutic index. The risk of overdose is present and should be anticipated. This is a real difficulty with the target population, which is elderly with risks of renal failure or hepatic failure. This population is also very often multi-medicated and there are a risk many drug interactions. Nevertheless, the review by the American Heart Association (AHA) and other data issued from clinical trials listed by the Applicant, did not raise concern about the co-administration of colchicine and statin in patients without advanced renal disease.

For example, some antibiotics, by decreasing the metabolism of colchicine, increase its plasma concentration, leading to overdose, with toxic effects that can lead to death. In addition, other combinations are not recommended (ciclosporin, verapamil, protease inhibitors) or require precautions (VKA, HMG-CoA reductase inhibitors). But large placebo-controlled CV trials that included patients on moderate and high-dose statin therapy, showed a low incidence of myotoxicity (<1%) that was no different compared to those taking placebo.

The experience with DDIs associated with the use of colchicine in patients with CV disease therefore mirrors the experience of its use in Familial Mediterranean Fever (FMF) and in gout, thereby confirming that serious DDIs are rare when colchicine is administered at low doses, is not prescribed concomitantly with a few selective drugs (e.g., strong/moderate CYP3A4 inhibitors, strong P-gp Inhibitors, digoxin), and is used cautiously in patients with advanced liver or renal disease.

Despite that colchicine has no antidote, is not dialyzable, and carries a significant risk overdose, colchicine has been in clinical use for over 70 years and its safety profile is well-known. Generally, the most common GI symptoms (including diarrhea, nausea, vomiting and abdominal pain) are mild, transient, and reversible upon discontinuation of the drug or reduction of the dose. While a deliberate overdose of colchicine may be fatal in up to 10% of cases, judicious use of colchicine at doses of 0.5–1.0 mg daily has proven safe. Furthermore, in the 90% of patients who do not develop early treatment intolerance, long-term use at this dosage proved to be safe and well tolerated.

Given the knowledge about colchicine, the interactions with this active substance are well mentioned in the SmPC as well as precautions and contraindications and recommendation for special population (elderly, patients with renal or hepatic impairment).

Review of concomitant medications and assessment of renal and hepatic function should be performed prior to initiating treatment with colchicine.

In special populations such as the elderly, and patients with renal or hepatic impairment, the healthcare professional should consider the potential benefits and risks of low-dose colchicine treatment in the context of the patient's medical history and concomitant medication.

Patients should be carefully monitored for any signs or symptoms of toxicity.

Summary Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's* Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

Safety specification

Part II: Module SVIII - Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

According to the GVP module V rev 2, there is no important identified risk, Important potential risk or Missing information including in the summary of safety concerns as no additional pharmacovigilance activities or risk minimisation measures are required for the product.

Overall, the safety profile of colchicine is considered well established and the safety profile well known.

Pharmacovigilance Plan

Routine Pharmacovigilance Activities

Colchicine has been used extensively for the treatment of gout and FMF. Thus, the risks and safety profile of colchicine have already been identified, and only routine pharmacovigilance activities are proposed. Routine pharmacovigilance activities will be employed for each identified and potential risk in Module SVII.

Routine Pharmacovigilance Practices include:

- Individual case safety report (ICSR) collection, processing and assessment.
- Medical review by healthcare professionals (including physicians) of all adverse events (AE) case reports.
- Expedited reporting to the Health Authorities of all applicable ICSRs as per current regulations.
- Routine literature screening of local journals for ICSRs and worldwide indexed journals for collection of new relevant safety data from published case reports, clinical studies, reviews or other publications.
- Benefit-risk assessment through annual Periodic Safety Update Reports (PSURs) with special emphasis on the listed safety concerns.
- Routine signal detection to monitor, detect and evaluate any new safety risks with colchicine.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

None

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date

The proposed renewal date is five years after the approval of this procedure.

IV BENEFIT RISK ASSESSMENT

Based on the pivotal study, the supportive studies and literature, colchicine can be considered effective for reduction of atherothrombotic events in patients with CAD after recent myocardial infarct, and addition to lipid regulation and platelet inhibition therapies.

Indeed, in the COLCOT study, the primary analyse has been reached with an analysis concluding to a reduction of 23% of the primary composite efficacy endpoint in the colchicine group, with a statistically significant difference between the treatment groups (131 events (5.5%) vs 170 events (7.1%) ; HR: 0.77; 95% CI, 0.61 to 0.96; p=0.02).

Furthermore, in the primary composite efficacy endpoint, the components CV death, resuscitated cardiac arrest, acute MI and stroke are hard clinical events, predictive and robust components. The component Urgent Hospitalization for Angina Requiring Coronary Revascularization (UHARCR) includes only the most severe and urgent clinical events, leading to an unplanned coronary revascularization procedure. According to literature, these events were associated with a higher risk for subsequent rehospitalizations, both all-cause and cardiovascular. They were also blindly adjudicated by an independent Clinical Endpoint Committee.

The composite secondary endpoint (composite of CV death, cardiac arrest, acute MI or stroke), including all components of the composite primary endpoint except the UHARCR component, was not significantly reduced in the colchicine group (111 events (4.7%) in the colchicine group, as compared with 130 events (5.5%) in the placebo group; HR 0.85; 95% CI, 0.66 to 1.10, p=0.22) but results showed a trend in the right direction for all the components.

Almost the same tendency was seen also in the supportive studies. Even not exactly in the same time frame, the supportive studies can confirm the efficacy of colchicine in patients with CAD after recent MI, in addition to standard therapies for the reduction of CV events.

The time frame of treatment was of 0 to 30 days post-MI in the COLCOT study, which has been assessed in 3 periods, but the other studies LODOCO/LODOCO2 provided interesting data only for patients treated with colchicine around 6 months to more than 2 years after the index event. According to the pivotal study, pos-hoc analyses revealed that the beneficial effects were better with early initiation of colchicine, from day 0 to 3, immediately after the index event, in-hospital. Furthermore, France and Germany were the countries with the greater rate of patients recruited within the 0-3 days period, compared with the American countries which had a greater number of patients recruited within the 8-42 days period. Therefore, according to clinical practice, the obvious time to start colchicine treatment should be preferably in hospital, at the time of presentation with an acute coronary event.

Considering the limited data on efficacy and more especially the low number of events after 2 years of treatments, and the absence of significant difference between groups, the benefit of a prolonged duration of treatment is not totally demonstrated. However, there is no reason to limit the treatment duration of a chronic treatment in the prevention of major adverse cardiovascular events.

Patients characteristics were quite homogenous and well representative of CAD disease.

Furthermore, the possibility to restrict target population to patients who would have the highest benefit/risk ratio has been discussed. Such subgroups of patients are difficult to distinguish according to the provided efficacy results.

In patients with prior MI, the results do not favor the group treated with colchicine in the COLCOT study. The confidence intervals are very large, and therefore the estimation points are not very informative. Regarding the Hazard Ratio (HR) estimate for the primary endpoint, even though its confidence interval extends down to 0.7 (lower limit), the point estimate is above 1, and the upper limit of the confidence interval at 1.58 is very unfavorable.

However, the cardiovascular benefit of low-dose colchicine treatment in patients with recurrent CVD events, is endorsed, in light with the results of the supportive LODOCO2 study on the primary efficacy endpoint, in patients with stable coronary disease, regardless of history and timing of prior acute coronary ischemia.

The indication wording “Prevention of ischemic cardiovascular events in patients with atherosclerotic coronary artery disease and recent myocardial infarction (MI), in addition to standard therapies” is therefore considered sufficiently informative.

Regarding the Risk, several points can be considered solved:

Firstly, results regarding non-CV mortality, taking into account the 2 larger studies in size, COLCOT and LODOCO2 (4745 patients in COLCOT and 5522 in LODOCO2), with adequately long term follow-up of patients, it can be concluded that there was no significant difference among study arms. In the COPS study, the higher rates of non-CV deaths seen may be attributable to imprecision based on the few events for analysis. In this study, the cause of non-CV death was in majority related to sepsis, while these patients in the colchicine group discontinued study medication within the first 30 days and were not taking colchicine at the time of death.

Furthermore, there was no significant difference in mortality of all causes between patients randomly assigned to receive colchicine or placebo in the 10,267 patients included in the COLCOT and LoDoCo2 studies, and also numerically less CV deaths in the colchicine group compared to the placebo group in both studies.

Regarding other results of concern, in the COLCOT study, evaluation of the exploratory endpoints showed no clinically relevant differences between treatment groups in terms of time to event for DVT/PE and heart failure hospitalization. The exploratory efficacy analysis shows that DVT or PE were the less frequent events without statistical differences between the colchicine and placebo group (respectively, 10 vs 7). Heart Failure Hospitalization showed a similar result when incidence data were compared between the treatment groups, with less hospitalizations for heart failure in the colchicine group than in the placebo group (32 vs 41). In the LODOCO2 study, the results with respect to the occurrence of DVT or PE or both, did not differ significantly between the trial groups (17 vs 16).

Otherwise, as expected, the most common adverse events reported in these studies were gastrointestinal (diarrhoea, vomiting, abdominal pain). Infections (2.2% vs 1.6%), neoplasms (2% vs 1.9%) and pneumonia (0.9% vs 0.4%) were other main serious adverse events reported. In COLCOT, a large reduction (>65%) in hs-CRP and WBC counts also occurred over the first 6 months post-MI in both treatment groups, as expected, without a significant difference between the groups.

Also, since colchicine has a narrow therapeutic index, the risk of overdose is present and should be anticipated. This is a real difficulty with the target population, which is elderly, with risks of renal failure or hepatic failure.

This population is also very often multi-medicated and there are many drug interactions. For example, some antibiotics, by decreasing the metabolism of colchicine, increase its plasma concentration, leading to overdose, with toxic effects that can lead to death. In addition, other combinations are not recommended (ciclosporin, verapamil, protease inhibitors) or require precautions (VKA, statins).

Colchicine has no antidote, is not dialyzable, and carries a significant risk of death in the event of overdose.

Moreover, because of too much high number of cases of colchicine intoxication, the ANSM has asked to the MAHs of products containing colchicine for a warning message to be added to the packaging of these products on 1st July 2023. The following message is:

If you experience diarrhoea, nausea or vomiting, consult your doctor immediately. (Bold font and red box)

To reduce this risk of overdose in patients taking colchicine for cardiology indications, the MAH was requested to provide updated mock-ups with this alert message. The MAH provided the updated labelling with this wording.

Based on the benefit risk assessment, it is possible to conclude that the BR of colchicine in the claimed indication, for CV prevention in patients with recent myocardial infarction, can be considered

positive.

Update D210: a Break Out Session was held on D209, following DE comments received at day195.

The FR position was not supported by CMS DE who raised a PSRPH at day 195 (summarised):

Potential serious risk to public health:

A positive benefit risk balance has not been demonstrated for the entire group of patients included in the proposed indication. The concerns are mainly due to consistent findings of an increased non-cardiovascular mortality in several clinical studies. In a recent metaanalysis (Zijun et al., 2022) the increase in non-CV mortality almost reached statistical significance (RR: 1.38, $p=0.05$) and was associated with an unfavourable imbalance in all-cause mortality (RR 1.07, n.s.). This signal although consistent, is not well understood and assumptions about an impact of tubular depolymerisation on immune- and other cells remain speculative. The trend for an increased rate of non-CV deaths was consistent over most subgroup analyses that were provided in the metaanalysis, supporting the robustness of the result.

From the data available, it cannot be concluded that the safety is in an acceptable range. This pertains especially to the increased rate of non-cardiovascular deaths in 3 out of 4 studies, the pivotal LoDoCo2 study, the COLCOT study and in the COPS study, with increased all-cause mortality in the study by Nidorf et al., 2020 and in the COPS study.

The concern of an increase in non-CV death is in line with the results of a recent Meta-analysis cited by the Applicant in the response document (Zijun Ma et al., Front. Cardiovasc. Med. 2022). The authors of the Metaanalysis concluded that colchicine overall had no significant effect on CV mortality and all-cause mortality. All-cause mortality was reported in 13 trials ($n = 13,288$), colchicine treatment was associated with a small numerical imbalance of a higher rate of death from any cause compared with controls (RR: 1.07; 95% CI: 0.85–1.36; p for heterogeneity $p = 0.56$; $I^2 = 19\%$; $p = 0.27$). Seven studies reported non-cardiovascular mortality. Colchicine was associated with a trend toward an increased risk of noncardiovascular mortality compared with controls being close to statistical significance. (RR: 1.38; 95% CI: 1.00–1.90; p for heterogeneity $p = 0.36$; $I^2 = 7\%$; $p = 0.05$). The signal of a trend for an increased rate of non-CV deaths was consistent over most subgroup analyses that were provided in the publication, supporting the robustness of the result.

The data are of concern. An in-depth assessment of mortality events and the reasons thereof is necessary in order to understand the relevance for the benefit risk balance in the overall population and possibly in subgroups of interest that may be prone to a higher risk. Based on the data provided it is not possible to assess, whether specific groups of patients have to be exempted from treatment, should be covered by warning statements or whether co-medications or identifiable medical conditions are relevant for non-cardiovascular mortality.

In summary, the published data indicate the potential for an increased risk of non-CV death in the target group of patients and in related patient populations. The finding underlines the need for a detailed analysis in the whole group and in subgroups. Based on the data presented, it is not possible to conclude on a positive balance between efficacy and safety in the target group of patients.

The concern has to be weighed in the context of a primary outcome of the pivotal COLCOT trial that is based on a primary composite endpoint that contains components that are generally not accepted in the regulatory context (UHARCR). For 3-MACE, (stroke, MI, CV/all-cause death) the result was not significant.

In conclusion, the strong and consistent signal of an increased non-CV death ($p=0.05$ in a recent metaanalysis) albeit not well understood might be attributable to non-specific cellular effects of colchicine. Over all studies the signal was associated with a numerical non-significant imbalance for all-cause mortality disfavouring colchicine. The data presented to not allow to identify patients at increased risk for such events. The concern is not sufficiently outbalanced by demonstrated efficacy in

COLCOT, considering that the primary endpoint result is to a considerable degree driven by UHARCR which generally is not accepted as a component of the primary efficacy endpoint in CV outcome trials. The Applicant is asked to discuss whether patients/subgroups at risk for non-CV death can be identified that may be reflected in the SmPC.

CMS DE raised also three other concerns (summarised below):

Other concerns:

1. Risk Management Plan

Other concerns not already raised by the RMS

In general, we agree with the conclusions of the RMS of the RMP. However, it should be noted that in DE in 2017/2018, due to fatal cases, extensive amendments were made to the PI (including changes of posology according to EULAR recommendation) and package size was reduced for nationally authorised products. A boxed warning at the top of the SmPC and PIL was added to the PI of the nationally authorised products in DE indicated for gout (at that time also used off-label for Familial Mediterranean Fever (FMF)) as routine risk minimisation measure with the following wording:

Important warning!

Because of the narrow therapeutic range of colchicine, the recommended maximum dose must not be exceeded. Overdosing, including by ignoring interactions, can lead to a fatal, very painful and irreversible poisoning with a fatal outcome. Please refer to sections 4.4, 4.5., 4.8 and 4.9 of this SmPC.

The medicinal product must be kept out of reach of others before and after use.

This boxed warning was also included in the SmPC and PIL during the marketing authorisation procedure for Colchicine Tiofarma (NL/H/3863/001/MR; Member States DE, AT, UK, IE, DK, NO, SE; EoP April 2017) indicated in gout and FMF. However, consideration should be given to including this warning for colchicin products with cardiologic indications in order to minimise fatal overdoses.

2. SmPC

Other concerns not already raised by the RMS

Proposed text for the sections on reproductive toxicity, use by women of childbearing potential/contraception in men and women and use in pregnancy, breastfeeding and information on fertility in the SPC (and PIL) for colchicine in the cardiovascular indication:

Rationale

Section 4.4 Women of childbearing potential/Contraception in males and females: Adaptation to SWP/NCWP RECOMMENDATIONS ON THE DURATION OF CONTRACEPTION FOLLOWING THE END OF TREATMENT WITH A GENOTOXIC DRUG“ EMA/CHMP/SWP/74077/2020 REV. 1*.

Section 4.6 – Pregnancy: Adaptation to the recommendations of the guideline 'FROM DATA TO LABELLING'.

Section 4.6 Breast-feeding: Adaptation to the recommendations of the guideline 'FROM DATA TO LABELLING'.

Section 4.6 Fertility: Adaptation to the recommendations of the guideline 'GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING EMEA/CHMP/203927/2005'.

3. PIL

Other concerns not already raised by the RMS : adaptation to the SmPC

Update D210:

As a result of the BOS, CMS DE was willing to consider the application approvable provided a sufficient response regarding reflection of the signal on non CV mortality in the SmPC and a commitment on close monitoring for mortality based among others on ongoing and published studies to come will be provided.

Following the discussion between the DE CMS, the Applicant and the RMS, the following measures were concluded :

Question 1:

- Update in SmPC/PIL:

The following paragraph has been added in the section 4.4 of the SmPC :

Other precautions :

Clinical trial data showed a trend for an increased risk of non-cardiovascular death in patients treated with colchicine. Although a clear association between colchicine therapy and non-cardiovascular death has not been established, caution should be exercised in colchicine-treated patients with chronic coronary disease and with comorbidities that may underlie potential causes of mortality. Weigh the potential benefits and risks and carefully monitor patients for any signs or symptoms of toxicity.

- Commitment:

The following commitment was concluded:

As per our current routine PV activities, Pharmascience International Limited, as MAH, commits to follow any new ADRs related to the specific safety concerns by reviewing them in the routine Pharmascience Signal Detection Meetings held every two weeks to determine whether or not any new safety signals can be identified and validated. Should any new safety signals be validated, the health authorities will be notified immediately in case any new or modified warnings may be required for either the Pharmascience Colchicine product or for all colchicine products in general marketed in the EU.

The definitive study results (with data analysis) of the two ongoing studies (CONVINCE (NCT02898610) and CLEARSYNERGY (NCT03048825)) should also be provided as soon as they are made available by institutional sponsors, through a post authorisation measure (variation).

Furthermore, regarding PSUR submission, the RMS will ask for 2 separate entries in the EURD list for this substance, since 1) it is not the same population, 2) not the same dosage (0.5mg in cardio indications and 1 mg in gout indications), 3) not the same duration of treatment (2 years in cardio indications vs 1 week to 3 months maximum in gout and other indications).

- Package sizes: the following comments will be considered at national level.

- Regarding the comment of the French authorities on the pack size of 90 tablets for hospital use only.

The following note will be added in the blue box during the national phase in France:

Hospital use only for the box of 90 and 100 tablets

- In DE, the smallest possible maximum package size will be considered taking into account the planned indication.

Question 2 (warning box in SPC and PIL)

The following paragraphs were concluded:

SmPC :

Important warning

Colchicine has a narrow therapeutic index, rendering it susceptible to significant risks of severe overdose. The recommended maximum dose must not be exceeded. The initial clinical manifestations of such overdose include gastrointestinal disturbances such as diarrhea, nausea, and vomiting. Depending on the ingested dose, potentially multiple organ failure may ensue, affecting various systems including respiratory, cardiovascular, hematological, and neurological. Patients should be made aware of these signs of potential overdosage, which may also occur if interactions are ignored. A reduction in dosage or discontinuation of treatment should then be considered. Please refer to sections 4.4, 4.5, 4.8 and 4.9 of this SmPC.

The medicinal product must be kept out of reach of others before and after use.

PIL :

Important warning !

The appearance of diarrhea (liquid stools more than 3 times a day) during treatment, accompanied or not by nausea and vomiting, may be the first signs of an overdose, which can be serious. If you notice these signs, contact your doctor immediately, who may reduce the dose or suspend colchicine treatment.

Do not exceed the recommended dose. Overdosing, including by ignoring interactions, can lead to very painful and irreversible poisoning.

Please refer to sections 2, 3 and 4 of this package leaflet.

[PRODUCT NAME] must be kept out of reach of others before and after use.

Questions 3 and 4 (texts update in SPC and PIL) : See directly in the Product Information for the final wordings regarding pregnancy.

V PROPOSED LIST OF OUTSTANDING ISSUES

V.1 Quality aspects

Major objections

Drug substance

None

Drug product

None

Other concerns

Drug substance (related to additional data provided by applicant only)

None

Drug product

None

V.2 Non clinical aspects

Major objections

None

Other concerns

None

V.3 Clinical aspects

Major objections

Pharmacokinetics

None

Pharmacodynamics

None

Efficacy / Safety

None

Pharmacovigilance system

None

Risk Management Plan

None

Other concerns**Pharmacokinetics**

None

Pharmacodynamics

None

Efficacy

None

Safety

None

Pharmacovigilance

None

Risk Management Plan

None

VI RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 Legal Status

VI.2 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Description	Due date

VI.3 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

The following commitment was concluded:

As per his current routine PV activities, Pharmascience International Limited, as MAH, commits to follow any new ADRs related to the specific safety concerns by reviewing them in the routine Pharmascience Signal Detection Meetings held every two weeks to determine whether or not any new

safety signals can be identified and validated. Should any new safety signals be validated, the health authorities will be notified immediately in case any new or modified warnings may be required for either the Pharmascience Colchicine product or for all colchicine products in general marketed in the EU.

The definitive study results (with data analysis) of the two ongoing studies (CONVINCE (NCT02898610) and CLEARSYNERGY (NCT03048825)) should also be provided as soon as they are made available by institutional sponsors, through a post authorisation measure (variation).

VI.4 Module I – Application related comments (including product name)

Product name

The name AJUSCAD 0,5 mg, comprimé pelliculé The name had been accepted in France.

But not “Myinfla 0.5mg, film-coated tablets” submitted Day 106 : The proposed name is too close to the names MYALEPTA (AMRYT PHARMACEUTICALS DAC) and MYFENAX (TEVA BV), which is not acceptable in the light of the following provisions of Article R. 5121-3 of the French Public Health Code: "without prejudice to the application of legislation relating to trademarks and service marks, the invented name shall be chosen in such a way as to avoid any confusion with other medicinal products and not to mislead as to the quality or properties of the medicinal product".

VI.5 Summary of Product Characteristics (SmPC)

The separately attached SmPC is considered acceptable.

VI.6 Package Leaflet (PL)

VI.6.1 Package Leaflet

The separately attached PL is considered acceptable.

VI.6.2 Assessment of User Testing

Readability test received

VI.7 Labelling

The separately attached labelling is considered acceptable.

VII APPENDIX

QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

PRODUCT INFORMATION

Name of the medicinal product:	
Name and address of the applicant:	
Name of company which has performed the user testing:	
Type of Marketing Authorisation Application:	
Active substance:	
Pharmaco-therapeutic group (ATC Code):	
Therapeutic indication(s):	

- Full user testing report provided ☒ yes ☐ no

- Bridging report provided ☐ yes ☒ no

- Grounds for bridging based on a sound justification:
☐ extensions for the same route of administration
☐ reference to test on same class of medicinal product
☐ reference to test with same safety issues
☐ other _____

Is the justification for bridging acceptable? ☐ yes ☐ no

Is the justification for not submitting a report acceptable? ☐ yes ☐ no

Reasons

1 TECHNICAL ASSESSMENT

1.1 Recruitment

- Is the interviewed population acceptable? ☒ yes ☐ no

Comments/further details _____

1.2 Questionnaire

- Is the number of questions _____ sufficient? ☒ yes ☐ no

- Questions cover significant (safety) issues for the PL concerned? ☒ yes ☐ no

Comments/further details _____

1.3 Time aspects

- Is the time given to answer acceptable? ☒ yes ☐ no
- Is the length of interview acceptable? ☒ yes ☐ no

Comments/further details _____

1.4 Procedural aspects

- Rounds of testing including pilot _____

Comments/further details _____

1.5 Interview aspects

- Was the interview conducted in well-structured/organised manner? ☒ yes ☐ no

Comments/further details _____

2 EVALUATION OF RESPONSES

2.1 Evaluation system

- Is the qualitative evaluation of responses acceptable? ☒ yes ☐ no
- Does the evaluation methodology satisfy the minimum prerequisites? ☒ yes ☐ no

Comments/further details _____

2.2 Question rating system

- Is the quantitative evaluation of responses acceptable? ☒ yes ☐ no

Comments/further details _____

3 DATA PROCESSING

- Are data well recorded and documented? ☐ yes ☐ no

Comments/further details _____

4. QUALITY ASPECTS

4.1 Evaluation of diagnostic questions

<Invented name>, <Procedure number>

Day 70-PrAR-O

