College ter Beoordeling van Geneesmiddelen

Public Assessment Report

Scientific discussion

Gloricard 0.5 mg tablets
(colchicine)

NL License RVG: 132800

Date: 15 July 2026

This module reflects the scientific discussion for the approval of Gloricard 0.5 mg tablets. The procedure was finalised on 1 December 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ASMF	Active Substance Master File
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine Kinase
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CV	Cardiovascular
CVD	Cardiovascular Disease
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HR	Hazard Ratio
(hs)CRP	High-Sensitivity C-Reactive Protein
ICH	International Conference of Harmonisation
MACE	Major Adverse Cardiovascular Event
MAH	Marketing Authorisation Holder
MI	Myocardial Infarction
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RCT	Randomised Controlled Trial
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TSE	Transmissible Spongiform Encephalopathy
ULN	Upper Limit of Normal

I. Introduction

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Gloricard 0.5 mg tablets, from Tiofarma B.V.

The product is indicated for: secondary prevention of atherothrombotic events in adult patients with coronary heart disease that has been stable for at least 6 months.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC, which concerns a full-mixed (complete dossier) application. The application is based on the Low-dose colchicine for secondary prevention of cardiovascular disease (LoDoCo2) trial and the complementary studies to this trial.

Colchicine is an anti-inflammatory drug originally extracted from the autumn crocus (*Colchicum autumnale*) and was used by the ancient Greeks and Egyptians. Colchicine has been used for decades and is authorised with the following indications:

- treatment of acute gout in adults.
- prophylaxis of a gout attack in adults during initiation of urate-lowering therapy.
- in Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis in adults and paediatric patients.

Recently, colchicine has been rediscovered for its potential use in the prevention of secondary cardiovascular events due to its anti-inflammatory properties. The key role of inflammation in the pathogenesis of coronary artery disease (CAD), has led to the exploration of anti-inflammatory agents for the prevention of secondary cardiovascular events. Colchicine modulates the innate immune system by inhibiting the activity of neutrophils, the activation of NLRP3 inflammasome, and the release of IL-1 beta. By reducing the activity of these components, colchicine can potentially stabilise atherosclerotic plaques and prevent cardiovascular events.

The MAH received scientific advice from the MEB in 2016 (prior to the start of the LoDoCo2 trial) and also in 2023.

II. Quality aspects

II.1 Introduction

Gloricard is a cream-white, round, flat faceted tablet with the inscription “0,5” on one side.

Each tablet contains as active substance 0.5 mg of colchicine.

The excipients are: microcrystalline cellulose E460, lactose monohydrate, sodium starch glycolate and magnesium stearate E572.

The tablets packed in white opaque polyvinylchloride (PVC) and aluminium blister in a carton box or in polypropylene (PP) white tablet container provided with a low-density polyethylene (LDPE) white space filler and a LDPE white lid in a carton box.

II.2 Drug Substance

The active substance is colchicine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Colchicine is a yellowish-white amorphous or crystalline powder and is very soluble in water and freely soluble in ethanol. The polymorphic form and particle size are not relevant as the drug substance is dissolved in ethanol during the wet granulation process.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The pharmaceutical formulation and manufacturing development of the drug product is considered acceptable in line with ICH Q8.

Manufacturing process
The manufacturing process consists of the following steps: dispensing and weighing of raw materials, wet granulation of the drug substance, drying of the granulate, lubrication, compression of tablets and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scale batches and additional blend and tabletting process validation has been provided for two full scaled batches, in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with their Ph.Eur. monograph. In addition, the functionality related characteristics for the excipients have been unambiguously laid down by the MAH in the application dossier. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, uniformity of mass, disintegration, hardness, friability, residual solvents, microbiological purity, identification, assay,

content uniformity, dissolution and related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. Although very low levels of nitrite or nitrate might be present in some of the excipients the conditions during the manufacturing process prevent formation of nitrosamine impurities. Since no aqueous solvents or solutions are used during the manufacturing process, and the occurrence of chemical reactions between solids is rare, the risk of nitrosamine formation can be considered low.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scaled batches and one full scaled batch from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three pilot scaled batches stored at 25°C/60% RH (36-60 months) and 40°C/75% RH (6 months). In addition, stability data on one full scaled batch has been provided stored at 25°C/60% RH (3 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 5 years. The labelled storage conditions are "Store below 25°C. Store blister pack or tablet container in the original cardboard packaging to protect against light.".

In-use stability data have been provided demonstrating that the product remains stable for at least 6 months following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Gloricard has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- To submit the mock-up prior to the commercialisation of Gloricard 0.5 mg tablets.

III. Non-clinical aspects

III.1 Introduction

As the application concerns a full-mixed application under the European Directive 2001/83/CE, no new non-clinical data have been submitted. The submitted non-clinical overview is based mostly on the publicly available scientific literature.

III.2 Pharmacology

As colchicine is a well-known substance with an extensive history of clinical use, no new pharmacological studies have been conducted by the MAH. No new studies are also considered required. The MAH has provided a summary of public *in vitro* and *in vivo* data on the pharmacological properties of colchicine based on public literature data.
Colchicine is an alkaloid with antimitotic activity that binds to the β-subunits of tubulin, thus preventing the polymerisation of α- and β-tubulin forms into microtubules (Bhattacharyya et al., 2008; Hastie, 1991). Disruption of normal cytoskeletal assembly leads to inhibition of many essential cellular functions including intracellular vesicle transport and secretion of mediators such as chemokines and cytokines. *In vivo*, colchicine was shown to reduce inflammatory response in several urate and carrageenan-induced rat paw inflammation models. The exact mechanism of colchicine in the treatment of gout is not completely established.
Literature describing a standard core battery of safety pharmacology studies is not available, however, the MAH provided an overview of published data on cardiovascular and central nervous system effects of colchicine. Data on respiratory effects were not found. This lack of information can be compensated by the long history of clinical experience.

III.3 Pharmacokinetics

Considering that colchicine is a well-known substance with an extensive history of clinical use for the treatment of gout, the provided information on pharmacokinetics is sufficient.
Absorption of colchicine is rapid. Colchicine distributes into many tissues, but primarily into bile, liver, spleen, and kidney. Colchicine also shows a preferential concentration in leukocytes. Colchicine levels in brain were very low (Hunter and Klaassen, 1975). Colchicine is metabolised to 2-demethylcolchicine, 3-demethylcolchicine and, to a lesser extent, 10-demethylcolchicine (Schönharting et al., 1974). Excretion of colchicine is primarily via the bile, whereas a minority is excreted via the urine (Hunter and Klaassen, 1974). Severe drug interactions may occur when colchicine is used with drugs that modulate the activity of the multidrug resistance efflux transporter P-glycoprotein or cytochrome P450 3A4 (Cada et al., 2010; Finkelstein et al., 2010; Guo et al., 2019; Imazio et al., 2009; Niel & Scherrmann, 2006; Nuki 2008; Richette & Bardin 2010; Sundy 2010; Terkeltaub 2009; Yang, 2010). This risk is sufficiently reflected in the SmPC and is in line with the SmPC of other colchicine products.

III.4 Toxicology

The toxicity of colchicine is well-understood due to decades of clinical experience. Adverse effects are in line with the mode of action as a microtubule inhibitor which affects cytoskeletal functions, cell movement and cell division. No new toxicity studies were required and the MAH provided published literature data on the non-clinical toxicity profile of colchicine.
Colchicine has a very narrow therapeutic margin. Main target organs of toxicity are the gastrointestinal (GI) tract and skeletal muscle. Colchicine was positive for genotoxicity in several tests. As colchicine prevents microtubule assembly by binding to tubulin, it is known to be an aneugenic substance which causes chromosome aberrations both *in vitro* and *in vivo*. Most experimental results indicate that colchicine is not clastogenic. No evidence of carcinogenetic potential was observed in animals. Colchicine negatively affects female and male fertility. Colchicine was also shown to be embryotoxic and teratogenic. The SmPC therefore mentions recommendations for the duration of contraception during and after colchicine treatment.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The MAH provided an experimentally determined log K_{ow} for colchicine of 1.03, derived from peer-reviewed literature, which is accepted. The PEC_{sw} was calculated based on a default F_{pen} and was 0.0025 µg/L.

Conclusions on studies:
Colchicine PEC surface water value is below the action limit of 0.01 µg/L and is not a persistent, bioaccumulative and toxic substance (PBT) substance as log K_{ow} does not exceed 4.5.

III.6 Discussion on the non-clinical aspects

The submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Gloricard is adequate.

IV. Clinical aspects

IV.1 Introduction

Colchicine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. Additionally, the MAH submitted the data of one new study on the exposure to colchicine in the cardiovascular disease patient population. The MEB agreed that this is sufficient in light of this mixed application.

IV.2 Pharmacokinetics

Absorption
Bioavailability of colchicine is about 40-50% (Rochdi et al., 1994; Ferron et al., 1996). Administration of colchicine with food had no effect on the rate of colchicine absorption, but it can decrease the extent of colchicine exposure by approximately 15-20%. Within the therapeutic dose range, colchicine exhibits linear pharmacokinetics (PK). Large inter-individual differences were observed between patients, intra-individual day-to-day variations were low. The large inter-individual differences were likely attributable to variability in absorption and metabolism.

Distribution
Colchicine is widely distributed across many tissues, with large values for the apparent volume of distribution.

Metabolism
Knowledge about metabolism of colchicine in humans is limited. CYP3A4, plays a key role in metabolising colchicine, which is metabolised to 2- and 3-demethylcolchicine (Tateishi et al., 1997).

Elimination
Colchicine has a relatively long terminal half-life. Renal clearance contributes to 10 to 30% of total clearance (Girre et al., 1989; Achtert et al. 1989; Rochdi et al., 1994; Ferron et al., 1996). It is postulated that enterohepatic recirculation and biliary excretion, mediated by P-glycoprotein, are the major routes of elimination.

Special populations

Patients with mild or moderate renal impairment or those actively receiving haemodialysis do not show accumulation of colchicine, whereas those with severe renal impairment show an estimated doubling of exposure (Wallace et al., 1991; Ben-Chetrit et al., 1998; Wason et al., 2012). Liver cirrhosis impairs colchicine clearance and demonstrated that the liver is a major route of colchicine elimination, however large inter-individual differences are observed between patients with impaired liver function (Wallace et al., 1970; Leighton et al., 1991; Rudi et al., 1994).

Colchicine is mainly metabolised by CYP3A4. Genetic polymorphisms in CYP3A4 could have a significant effect on the PK of colchicine. However, the clinical consequences of genetic polymorphisms in CYP3A4 are currently not clear for medicinal products and is most likely already captured by the inter-individual variability in the different clinical studies. Furthermore, colchicine is a substrate of P-glycoprotein. Genetic polymorphisms in P-glycoprotein are known, but the clinical consequences are currently not clear. Genetic polymorphisms in P-glycoprotein appear to affect the plasma levels of efavirenz, cyclosporin, tacrolimus, sirolimus (Olafuyi et al., 2021).

Extensive literature research has been conducted to examine the PK of colchicine in relation to gender, race and weight. Unfortunately, no relevant studies were identified. It is expected that exposure to colchicine is increased in elderly subjects, due to decreased renal function. Ethnic origin and body weight have not been systematically assessed in trials related to cardiovascular disease prevention. Overall, the effect of ethnic origin is expected to be limited but cannot be excluded, and already captured by the inter-individual variability in the different clinical studies. The effect of body weight on the exposure of colchicine in the LoDoCo2 study was not investigated. Thus, the effect of body weight on the PK remains unknown. The effect of body weight on the PK may be high, since it is known from other medicinal product that the exposure could be affected by body weight (with higher exposure in subjects with low body weight and lower exposure in subjects with a high body weight compared to the average body weight). Therefore, no statement can be made that body weight does not have a significant effect on the PK. Recommendations regarding the use of colchicine in special populations has been included in the SmPC.

Drug-drug interactions

Drug-drug interactions involving colchicine have been described in the literature. Most notably, dosage reductions are regarded necessary when colchicine is administered in subjects who receive concomitant treatment with CYP3A4 and/or P-glycoprotein inhibitors (see clinical part of this overview). Further, several cases of myopathy and rhabdomyolysis after concomitant use of colchicine and a statin have been reported. Information on drug-drug interactions has been included in the SmPC.

Clinical study in the patient population

The pivotal clinical efficacy and safety study (LoDoCo2) was conducted in the Netherlands and in Australia. The investigational product was produced for Australia by Aspen Pharmaceuticals (Colgout), the manufacturer of colchicine for the Dutch cohort was Tiofarma. The intended commercial formulation in the application is identical to the Dutch cohort colchicine Tiofarma product.

Colchicine is a BCS class III narrow therapeutic index compound. The formulation of Aspen and Tiofarma are not qualitatively the same or quantitatively very similar as stated in the EMA bioequivalence guideline. However, excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, are not present in both formulations. Dissolution studies were performed to investigate the similarity between the two formulations. Dissolution was investigated using the basket method at pH 1.2, 4.5 and 6.8 according to the European Pharmacopoeia standard 2.9.3. The clinical batches used in study LoDoCo2 were not investigated, but batches identically manufactured were used. This is considered acceptable. The dissolution is >85% in 15 minutes for both the Tiofarma and Aspen formulations. The differences in excipients are not critical and dissolution is rapid. Therefore, the two formulations can be considered similar.

In study LoDoCo2, the concentration at steady state was investigated for the Tiofarma and Aspen formulation. Serum levels were analysed in an Australian laboratory with a method based on solid phase extraction of colchicine from serum followed by LC-MSMS. The method was linear across the

calibration range of 0.05 µg/L to 10 µg/L. Validation requirements were met for intra- and inter-day precision and accuracy. Stability was shown for 24 hours at autosampler conditions, for 5 days at 4°C, for 3 weeks at -20°C. Colchicine levels at steady state were reported. However, blood samples from the Dutch cohort were analysed following a maximum storage period of 2.5 years which was outside the long-term stability period. It is not known if the colchicine is stable in plasma samples for a period of 2.5 years. It is therefore unknown if the measured concentrations are correct. However, it not likely that the pharmacokinetics in this cardiovascular disease population is different than other registered patient populations.

IV.3 Pharmacodynamics

The anti-inflammatory action of colchicine is suggested to be associated to preventing tubulin polymerisation, suppression of the activation of NLRP3 inflammasomes, inhibition of the expression of E-selectin on endothelial cells and prevention of neutrophil adhesion, amongst some other effects. Although the mechanism of action of colchicine in the secondary prevention of atherothrombotic events in patients with coronary artery disease is not fully understood, the available data on the pharmacodynamics of colchicine has been adequately summarised by the MAH. No new data have been submitted, which is acceptable given the legal basis under which it has been submitted.

IV.4 Clinical efficacy

The event driven study demonstrated a significant treatment effect on the 4-point major adverse cardiovascular events (MACE) of cardiovascular death, myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularisation (n=187 (6.8%) vs = 264 (9.6%), hazard ratio (HR) 0.69 (95% CI 0.57-0.83); p<0.001), driven by the MI and revascularisation endpoint, and the generally EMA guideline preferred secondary endpoint of 3-point MACE (n=115 (4.2%) vs n=157 (5.7%), HR 0.72 (95% CI 0.57-0.92); p=0.007), excluding the ''soft'' endpoint of ischemia driven coronary revascularisation. Further, a lack of additional post-trial benefits suggest for a need of continued use of colchicine to maintain its benefits.
However, the study was entirely driven by the 2 years earlier started Australian cohort, which included one third of the population with 2 times longer follow-up of 49 months (78/951 vs 147/953 , HR 0.51(95% CI 0.39-0.67)), with no evidence of any relevant effect in the larger but shorter 23 months followed-up Dutch subgroup (109/1811 vs 117/1847, HR 0.92 (95% CI 0.71-1.20)). This substantial difference in treatment effect is not understood. The MAH has been requested to clarify the difference, since it does not support the use of colchicine within the primary target population, which is the Dutch cohort.
Several possible explanations for the difference in treatment effect between the Australian and the Dutch cohort have been explored by the MAH. The difference in effect was not explained by any of the differences in colchicine product or clinical characteristics in the two regions.
In the Dutch cohort, patients were slightly younger and included a higher proportion of females and current smokers. In addition, there was a higher proportion of patients in the Netherlands with stage 3a renal dysfunction, atrial fibrillation, a history of revascularisation and acute coronary syndrome within the prior 24 months and those taking ezetimibe and beta-blockers compared to Australia. An effect modifier analysis was used to identify the impact that clinical characteristics and therapy at baseline may have had on the interaction between region and the effect of colchicine. In total, 19 baseline characteristics, commonly reported in cardiovascular trials were included. This analysis showed that the minor differences in clinical characteristics and concomitant medical therapies were insufficient to explain the observed differences in treatment outcome.
The follow-up time of the Australian cohort is substantially longer compared with the follow-up time of the Dutch cohort, but that in itself does not explain the differences found in treatment effect.

Since exploring all plausible reasons that could have explained the difference in treatment effect between the two regions did not lead to any solid conclusions, this issue is considered a chance finding and will not be further pursued.
For any other subgroups, in general subgroup analyses were consistent with the primary analysis, including patients on high vs low dose of statins or using ezetimibe. Although, for some subgroups including e.g. age, smoking, diabetes, insulin dependency, renal function the results appear counterintuitive. Nevertheless, any chance finding cannot be excluded due to the low numbers and wide confidence intervals of these subgroups.
The results for exploratory endpoints of the occurrence of new onset or first recurrence of atrial fibrillation, deep-venous thrombosis or pulmonary embolism or both, and new-onset diabetes did not differ significantly between treatment arms.
With regard to the statistical plan, the assumptions of the sample size calculation were reasonable and the calculation can be followed. The definition of the study populations is considered acceptable, as is the post-hoc definition of the intention-to-treat population, which is considered more adequate. The statistical analysis of the endpoints are considered standard and acceptable. However, the analyses assume non-cardiovascular death is non-informative, which is not readily agreed, especially since non-cardiovascular death appears more prevalent in the colchicine arm. In this respect, a numerical increase for colchicine vs placebo was seen for overall mortality (n=73 (2.6%) vs n=60 (2.2%), HR 1.21 (95% CI 0.86-1.71), which was driven by an increase in non-cardiovascular mortality (n=53 (1.9%) vs n=35 (1.3%), HR 1.51 (95% CI 0.99-2.31). Since the primary endpoint did not include mortality other than cardiovascular, the increase of non-cardiovascular death is of concern. Two sensitivity analyses were provided, using a cause-specific model and a Fine and Gray sub-distribution model, testing the effect of non-cardiovascular death as competing risk in the primary endpoint analysis. These analyses indicated a negligible effect of non-cardiovascular death on the results. Of note, the MAH did not provide an analysis incorporating non-cardiovascular death in the primary endpoint composite definition, but considering the analyses already provided this is not further pursued. Understanding of the non-cardiovascular events is further discussed in the safety section.
The suggested anti-inflammatory effect of colchicine has been described in the pharmacology section, but is not exactly and entirely clear. Any previous medicinal products which would show a cardiovascular (CV) risk benefit based on an anti-inflammatory effect have currently not been approved, because of an inappropriate understanding of the effect (in relation to its mechanism) or due to an insufficient demonstration of a beneficial effect (e.g. canakinumab, methotrexate). The association between elevated (high-sensitivity) C-reactive protein ((hs)CRP) and cardiovascular outcomes was assessed by Burger et al., as provided by the MAH. Increased levels of CRP were associated with the risk of recurrent cardiovascular disease (CVD), and this association was strongest for patients with CAD.
Nevertheless, it is yet unclear if treating high levels of hsCRP will consequently lead to lower CV risk. Provided publications by the MAH did not robustly demonstrate this association, due to important limitations in these studies to sufficiently support such an association. The effects of colchicine on plaques in the study of Fiolet et al. (2025) were mixed; no difference in pericoronary adipose tissue (PCAT) attenuation was found between patients treated with colchicine and those with placebo, the calcium plaque volume and burden were statistically significantly higher in patients on colchicine compared with patients on placebo, but there was no difference in non-calcified plaque burden. The study is limited by the cross-sectional nature, but may provide hints on the possible effects of colchicine on atherosclerotic plaques.
At baseline, typical medication in CAD were used with antiplatelet agents or anticoagulants, lipid-lowering agents, beta-blockers, and renin-angiotensin-aldosterone system (RAAS) inhibitors being used by 99.7%, 96.6%, 62.1% and 71.7% of subjects, respectively. An effect modifier analysis was used to identify the impact that clinical characteristics and therapy at baseline may have had on the interaction between region and the effect of colchicine. In total, 19 baseline characteristics, commonly reported in cardiovascular trials were included. This analysis showed that the minor differences in clinical characteristics and concomitant medical therapies were insufficient to explain the observed differences in treatment outcome.

In the study, 96.6% of patients were taking a lipid-lowering agent. The combination of colchicine with an HMG-CoA reductase inhibitor (statin) could potentially increase the risk of myopathy and rhabdomyolysis due to CYP3A4 inhibition and additive toxicity. This has been reflected in the SmPC, and no additional measures have been taken in the LoDoCo2.
Since an unambiguous CV protective treatment effect of colchicine in a CAD population has not been clearly demonstrated based on the LoDoCo2 study and literature studies, the Applicant has provided further evidence based on literature data of meta-analyses and several clinical studies.
The MAH provided the results of two meta analyses that assessed colchicine for secondary prevention of vascular events. D'Entremont et al. included studies all randomised controlled trials (RCTs) comparing colchicine with no colchicine on top of the system organ class (SOC) in atherosclerotic cardiovascular disease patients, with treatment duration >90 days. Samuel et al. restricted to studies reporting at least one of the following outcomes: cardiovascular death, MI, stroke, cardiac arrest, or urgent coronary revascularisation, and treatment duration was >12 months. Specifically for the outcome prevention of MACE, the COLCOT, COPS, LoDoCo2, and CLEAR study were included in both Samuel et al. and d'Entremont et al., whereas Lodoco, CONVINCE and CHANCE3 were included only by d'Entremont. D'Entremont et al. reported a relative risk of 0.88 (95% CI 0.81-0.95) for prevention of MACE and Samuel et al. reported a HR of 0.75 (95% CI 0.56-0.93) for prevention of MACE. In both meta-analyses, no difference was made between use of colchicine in the acute phase after a CV event, or the stable phase, such as LoDoCo2.
Further support may be derived from the COLCOT study. In contrast to the LoDoCo2 trial, the supportive large COLCOT trial, which included 4745 patients within 30 days (mean 13.5 +/- 10.1 days) after a myocardial infarction, largely fills the post-MI spectrum from acute to chronic history of MI, for initiating colchicine. The study demonstrated significant beneficial treatment effect in the primary composite efficacy endpoint (HR 0.77 (95% CI 0.66-.96), p=0.02), although this effect was primarily driven by a reduced incidence of strokes and urgent hospitalisations for angina leading to coronary revascularisation. A consistent effect was found with the general EMA guideline preferred MACE-3 endpoint (CV death, MI, stroke) excluding the soft revascularisation endpoint, (HR 0.85 (95% CI 0.66-1.10)), although statistical significance was not reached. Nevertheless the study was limited by the fact that no Dutch patients were included.
The LODOCO study appears to show a beneficial effect in a population comparable to the LoDoCo2, but was considered of only little support due to its exploratory nature.
The CLEAR study was a multicentre RCT in which patients who had a myocardial infarction were randomised as soon as possible after their MI between colchicine 0.5 mg or placebo. The primary efficacy outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularisation, evaluated in a time-to-event analysis. A total of 7062 patients at 104 centres in 14 countries underwent randomisation. A primary-outcome event occurred in 322 of 3528 patients (9.1%) in the colchicine group and 327 of 3534 patients (9.3%) in the placebo group over a median follow-up period of 3 years (HR 0.99; 95% CI 0.85-1.16; p=0.93).
The CLEAR study was partly performed during the COVID-19 pandemic which might have affected the results. Before the start of the pandemic, a 22% reduction in the incidence of the primary end point in the colchicine patients was seen compared with the control group, whereas this reduction was lost during the pandemic. The ratio MI/all-cause mortality of 0.62 might indicate that MIs were less seen, which affected the trial towards a neutral result.

IV.5 Clinical safety

In general, the safety profile of colchicine is well-known, although currently it is used in a different population and generally a lower dose than the approved colchicine products. The safety profile for the existing indications is associated with GI symptoms, haematological adverse events (AEs), muscle related AEs, an dermatological AEs. These have also been described based on post marketing data.

For the pivotal LoDoCo2 trial, a selective approach to safety data collection was utilised including reporting of serious adverse events and adverse events of special interest, which was agreed upon by the MEB during a previous scientific advice. With a 49.3 months in the Australian cohort and 22.6 months in the Dutch cohort, long-term exposure could be considered, although for the Dutch cohort this is relatively limited.

As previously mentioned, a selected population, able to tolerate colchicine has been included in the study due to the run-in phase, which could somewhat limit the safety interpretation. This is included in the SmPC. Consequently, during the randomisation phase, a limited number of 589 (10%) subjects permanently discontinued study medication, due to side effects (3.5% vs 3.5% for colchicine vs placebo) , patient choice (4.7% vs 4.9%), or due to illness or death (0.8% vs 0.8%). The most frequently discontinuation due to AEs was in the SOC of gastro-intestinal disorders (0.4% vs 0.4%).

During the randomised period, a substantial number of (serious) adverse events were reported in 44.5% vs 45.7% of subjects on colchicine vs placebo, respectively, although comparable across treatment arms. Reassuringly, comparable numbers of at least one serious adverse event (SAE) were reported in 13.9% vs 14.9% of subjects, respectively.

Most frequently reported SAES were death (2.6% vs 2.1%, for colchicine vs. placebo), non-cardiac chest pain (0.7% vs 0.9%), infections (2.9% vs 2.6%), mainly cellulitis (0.6% vs 0.2%), lower respiratory tract infections (0.9% vs 1.2%), and coronary revascularisation (0.6% vs 1.2%). No signs of increased risk for (hospitalisation for) infections (5.0% vs 5.2%) or pneumonia (1.7% vs 5.2%) were reported (based on published data), or an increased risk for cancer (4.3% vs 4.4%). While, in the COLCOT including patients with recent MI, for hospitalisations for pneumonia, and hospitalisation for infections, a higher frequency was seen. Data in the Andreis meta-analysis report an incidence for infections in three studies of 4.7% in patients receiving colchicine vs. 4.7% in patients on placebo (P=0.90, pooled risk ratio 1.02, 95% CI 0.77–1.34) and mentions the significantly increased risk for pneumonia as reported in the COLCOT study. A systematic review and meta-analysis by Stewart et al. examined the side effect profile of colchicine systematically in controlled clinical trials across all published indications. On the subject of infectious events, seven studies reported various infectious events, including urinary tract infection, parotiditis, shingles, upper respiratory tract infection, nasopharyngitis and sinus congestion. From these papers, 0.4% (95% CI 0.2, 0.6) of participants using colchicine reported an infectious event compared to 2.1% (95% CI 1.6, 2.7) of participants in comparator groups. The overall risk ratio (95% CI) of infectious events in colchicine users compared with pooled comparator groups was non-significant: 1.03 (0.70, 1.51). The difference between placebo and active comparator groups was not significant (P=0.94). Moreover, the recent study of Jolly et al. reported similar frequencies of serious infection between patients treated with colchicine (n=87, 2.5%) and patients treated with placebo (n=101, 2.9%) (hospitalisations for infections and pneumonia were not reported as such). The increase in frequency of hospitalisations for infections and pneumonia in the COLCOT study was not confirmed in other studies. No obvious increased risk of infections was seen in the studies, which is reassuring.

Hospitalisation for GI symptoms were comparable (1.9% vs 1.8%, based on published data). However, the meta-analysis of Andreis et al. 2021 showed a significant increased risk for GI symptoms (HR 1.67 (95% CI 1.20-2.34), in particular shortly after treatment. Similarly, in a meta-analyses of Fiolet, including the LoDoCo2, COPS and COLCOT studies, a numerical increase in hospitalisation for GI symptoms was seen, both in the LoDoCo2 and COLCOT.

In the Dutch cohort of LoDoCo2, some increase of frequency was seen for atrial fibrillation (1.5% vs 1.2%), however, any new onset of AF or atrial flutter, evaluated as a secondary endpoint, was not reported to be higher (1.7% vs 2.0%).

With regard to adverse events of special interest, myopathy was slightly increased with the use of colchicine (14.0% vs 12.2%), but for myositis in 0.1% vs 0.1%, and rhabdomyolysis in 1 subject on colchicine, frequencies were low. For the Dutch cohort, myalgia was also reported at a higher frequency for colchicine (21.2% vs 18.5%). A meta-analysis of Andreis et al. also showed an increased risk for GI symptoms (HR 1.67 (1.20-2.34), in particular shortly after treatment, and a significant increase in myalgia (HR 1.16 (1.02, 1.32). Further, a mild elevation of creatine kinase (CK) was seen on colchicine (123 U/L vs. 110 U/L; p <0.01) and the end of study in the sub-study of 1176 patients in LoDoCo2. Five

(0.6%) participants in the colchicine group and two (0.2%) participants in the placebo group had moderately elevated CK levels (5-10 x upper limit of normal (ULN)). Only one (0.1%) participant in this cohort, who was taking colchicine, had markedly elevated CK levels (> 10 × ULN). So, only a slight increase in muscle related symptoms were observed, despite that 96% used statins. Therefore, a warning statement on concomitant use is stated in the SmPC.
For any other adverse event of special interest, no difference between treatment groups was reported. Peripheral neuropathy was reported in 5.2% vs 5.5%, and neutropenia in 0.1% vs 0.1% of subjects. Gout was less prevalent in the colchicine group as expected (1.4% vs 3.4%, based on published data). For the Dutch cohort, dysesthesia was comparable between treatment arms (7.9% vs 8.3%).
All-cause mortality was more prevalent in the colchicine arm, although no statistically significant difference was seen (n=73 (2.6%) vs n=60 (2.2%), HR 1.21 (95%CI 0.86-1.71). This increase was attributed to a numerical increase of non-cardiovascular mortality on colchicine (n=53 (1.9%) vs n=35 (1.3%), HR 1.51 (95% CI 0.99-2.31), while a numerical improvement was seen for cardiovascular mortality (n=20 (0.7%) vs n=25 (0.9%), HR 0.80 (95%CI 0.44-1.44).
Non-cardiovascular mortality was described in more detail in the supplementary paragraph of the original publication in the New England Journal of Medicine. The causes of the non-cardiovascular mortality were diverse and did not indicate for any pattern, which can be regarded as somewhat reassuring as this may suggest that no specific underlying off-target effect is responsible. However, similar to the LoDoCo2 study, in the COPS study a numerical increase in non-CV mortality was seen, although numbers were low. In LoDoCo2, cancer (0.9% vs 0.8%) and end stage pulmonary disease (0.3% vs 0.1%) were the most common non-cardiovascular causes of mortality and numerically higher in the colchicine group. Infection causing mortality occurred in 0.1% vs 0.1% of subjects. The pooled analysis in the meta-analysis of Fiolet et al. (including the randomised, placebo-controlled, double-blind trials LoDoCo2, COLCOT, COPS and the trial by Deftereos and the open-label trials with blinded endpoint adjudication CONVINCE and LoDoCo) showed no significant increases in cardiovascular, non-cardiovascular or all-cause mortality.
In a sub-study of the LoDoCo2 study, blood samples were taken at the close-out visit in a subgroup of 1176/5522 participants in Australia and the Netherlands with median exposure of study drug of 32.7 (24.0-48.6) months. Markers of renal function (serum creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR)), liver function (alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), bilirubin, albumin), and CK levels were determined. On colchicine, no significant changes were seen in creatinine, blood urea nitrogen (BUN), and eGFR, also compared with placebo.
Compared with placebo, colchicine was associated with a slight elevation in ALT (30 U/L vs. 26 U/L; p <0.01). Most elevations in ALT were mild (< 5 x ULN) in both treatment groups, with increased frequency on colchicine (246/ (27.5%) vs 153/ (17.4%). There were no moderate to marked ALT elevations (> 5-10 × ULN) in both treatment groups.
A small (median) decrease in leukocytes from 6.99 x 109/L to 6.62 x 109/L and thrombocytes from 237.5 x 109/L to 231.0 x 109/L was seen. However, incidentally severe clinically relevant leukopenia has been reported. Although thrombocytopenia was not more prevalent in LoDoCo2, it was noted that thrombocytopenia has been included in section 4.4 of some authorised SmPC (e.g. Colchicine Ria 0.5 mg tablets, NL/H/4121/001). Also, in the meta-analysis of Andreis a numerical increase in haematology AEs was (HR 1.39 (0.68-2.84)) was reported. However, a warning statement on haematology adverse effect risk has already been included in the SmPC.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Gloricard. At the time of approval, the most recent version of the RMP was version 0.2 dated 13 November 2024.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, the MAH provided a clinical overview, which is based on scientific literature. The MAH also submitted the data of one new study on the exposure to colchicine in the cardiovascular disease patient population. Risk management is adequately addressed. The clinical aspects of this product are approvable.

V. User consultation

The MAH has explained that the 'parent' and 'daughter' package leaflet are sufficiently similar for bridging. The already conducted and approved by the MEB readability test for Colchicine Tiofarma 0.5 and 1 mg tablets together with a short discussion provided by the MAH on the differences between the patient information leaflet for Colchicine Tiofarma 0.5 and 1 mg tablets (parent) and for Gloricard (daughter) is considered sufficient. The request of the MAH for the Waiver for Consultation with Target Patient Population is also considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gloricard 0.5 mg tablets have a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

In the Board meeting of 25 September 2025, the following was discussed:

Third round, Clinical studies
The major objections from the previous round have been resolved.

- It was previously noted that the effect seen in the various studies is inconsistent. Since then, meta-analyses have been conducted that generally indicate a beneficial effect of colchicine in coronary heart disease. During the proceedings, the results of the CLEAR study were added to the file. This study shows no effect in patients with acute myocardial infarction (MI). An explanation given by the MAH is that this study was partly conducted during the COVID-19 pandemic, and that there was underreporting of MI during that period. An effect is indeed seen in the pre-COVID period. The Board notes that the argument of underreporting is not strong. It is more plausible that there were actually fewer cases of MI during the COVID-19 pandemic due to the lower infection pressure resulting from the infection-limiting measures that were introduced in the context of the pandemic.
  Regarding the observed regional differences in efficacy in the LoDoCo2 study, it is noted that this remains unexplained. It was investigated whether a baseline difference in treatment (between Dutch and Australian patients) underpinned this, but no results were obtained. It is considered highly likely that the regional difference in efficacy is a chance finding. It is decided that this will no

longer be regarded as a major objection, partly in view of the meta-analyses that indicate a positive effect.

- Regarding the use in the elderly, it was noted that the SmPC did not make it clear that the average age of the patients in the LoDoCo2 study was 67 years. It was also not stated that efficacy had not been demonstrated in patients aged 80 years and older. It was argued that this information, which is important for the prescriber, should be included in the SmPC. The MAH has added this information to the SmPC.
- In the first round, it was noted that there are indications that colchicine may interact (adversely) with statins, and that no information regarding this was included in the SmPC. A number of questions were raised regarding this. This has led to an adjustment of the product information.

Conclusion
The Board is positive regarding this medicine. The major objections from the previous rounds have been resolved.

The MEB, on the basis of the data submitted, considered that the overall benefit-risk balance of Gloricard is considered positive, and have therefore granted a marketing authorisation.

The national procedure was finalised with a positive outcome on 1 December 2025.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.