COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Colchicine DMB 0.5 mg and 1 mg, tablets

(colchicine)

NL/H/5248/001-002/MR

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This module reflects the scientific discussion for the approval of Colchicine DMB 0.5 mg and 1 mg, tablets. The procedure was finalised at 4 March 2021 For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FMF	Familial Mediterranean Fever
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
WHO	World Health Organisation

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Colchicine DMB 0.5 mg and 1 mg tablets from Tiofarma B.V (The Netherlands).

Colchicine DMB can be used for the following therapeutic indications:
Gout

- Colchicine is indicated in adults for the treatment of acute gout
- Colchicine is indicated for the prophylaxis of a gout attack during initiation of urate-lowering therapy.

Familial Mediterranean Fever

- Colchicine is also indicated in adults and children with Familial Mediterranean Fever (FMF) for the treatment of prophylaxis of attacks and prevention of amyloidosis.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of colchicine. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety.

The concerned member states (CMS) involved in this procedure were Belgium, Spain and Portugal.

Scientific advice
The MAH received scientific advice from the Medicines Evaluation Board (MEB) in 2014 regarding comparability of Tiofarma 0.5 mg and 1 mg tablets with Colcrys (0.6 mg colchicine/tablet). Also, a request for a biowaiver between Tiofarma 0.5 mg and 1 mg tablets was discussed.

II. QUALITY ASPECTS

II.1 Introduction

- Colchicine DMB 0.5 mg tablets are off-white, round, flat tablets with facet with the inscription “0,5” on one side.
- Colchicine DMB 1 mg tablets are off-white, oval tablets with the inscription “C1C” on one side.

Each tablet contains as active substance either 0.5 mg or 1 mg of colchicine.

The tablets are packed in PVC/Alu blisters and in polypropylene containers.

The excipients for Colchicine DMB are microcrystalline cellulose (E460), lactose monohydrate, sodium starch glycolate and magnesium stearate (E572).

II.2 Drug Substance

The active substance colchicine is an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is very soluble in water, rapidly recrystallising from concentrated solutions as the sesquihydrate; freely soluble in alcohol and chloroform and practically insoluble in cyclohexane. Colchicine must be protected from light. Particle size and polymorphism are not relevant as the drug substance is first dissolved during the drug product manufacturing.

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 drug substance specification is in line with the Ph. Eur. monograph, with an additional requirement for 'any other impurity', as required by the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two production scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the conditions covered by the CEP. 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 development of the product has been described, the choice of excipients is justified and their functions explained.

The 1 mg tablets are fully dose proportional with the 0.5 mg tablets, prepared from a common blend. The dissolution profiles of the both strength are comparable in all media (water, and buffers at pH = 1.0, 4.5, and 6.8) and dissolution is very rapid (>95% within 5 min) in all cases. The dissolution data support the biowaiver of strengths. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

Colchicine DMB 0.5 and 1 mg tablets are manufactured by essentially the same manufacturing process as the tablets are produced from a common blend. The product is manufactured using conventional manufacturing techniques (wet granulation) and the process consists of the following steps: weighing of raw materials, dissolution of active compound, mixing, drying, sieving, tabletting and packaging. The manufacturing process has been adequately validated, according to relevant European guidelines, using traditional process validation. It is regarded as a non-standard process for both strengths since the tablets contain less than 2% Colchicine. Consequently, full production-scale data for two batches of the 0.5 mg tablets and one batch of the 1 mg tablets have been provided. Based on these data it can be concluded that the manufacturing process of Colchicine tablets is controlled and consistently demonstrates compliance to the finished product specifications.

Control of excipients

The excipients comply with the Ph. Eur. They are well known and their specifications are acceptable.

Quality control of drug product

The control tests and specifications for drug product are adequate to control the relevant parameters for the dosage form. The product specification includes tests for appearance, average mass, uniformity of mass (at release), disintegration, hardness, friability, residual solvents (at release), microbiological purity (not routinely tested), identification, assay, uniformity of content (at release), dissolution, and related substances. For the 0.5 mg and the 1 mg tablets the release and shelf-life requirements and limits are identical and acceptable. The analytical methods have been adequately described and validated. Batch analysis results of three commercial scale batches of the 0.5 mg strength and three commercial scale batches of the 1 mg strength have been submitted. All batches comply with the proposed specifications.

Stability of drug product

Stability data on the product has been provided for three full-scale batches per strength stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/Alu blisters, or PP-containers, with PE closures. The stability results show that the tablets are stable when packed in containers at both conditions. When packed in blisters the hardness of the tablets rapidly deteriorated under accelerated conditions to below the acceptance limit, but stayed within specification under long term conditions up to 60 months. All other parameters showed no up or downward trends and stayed within limits. Based on the provided information the proposed shelf-life of 60 months with the storage condition “store

below 25°C, in the original packaging in order to protect from light" is acceptable. In-use stability has been demonstrated for a period of six months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM 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. The used lactose monohydrate is of animal origin but complies with the current TSE Directive.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Colchicine DMB has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Colchicine is a natural product which can be extracted from two plants of the lily family, i.e. from the genus Colchicum (usually called *Colchicum autumnale*) and from the *Gloriosa superba*. Originally used to treat rheumatic complaints and especially gouty attacks, it was also prescribed for familial Mediterranean fever. Hence, the clinical experience with colchicine is very extensive, and the clinical safety and efficacy of colchicine have been well documented. Colchicine has been most studied in relation to its action in gout patients and in patients with familial Mediterranean fever.

Gout is a well-known type of arthritis associated with impaired metabolism of purines, resulting in hyperuricemia and an accumulation of the metabolic end product urate, in the form of monosodium urate crystals, in joints. The build-up of these crystals induces an acute inflammatory response that involves leukocyte recruitment, in particular that of neutrophils. Aside from pain, patients are most concerned with the loss of mobility, as well as emotional stress, interrupted sleep, work and social limitations, and joint swelling and deformities. Colchicine is used for the treatment of acute gout flares and the prophylaxis of gout flares.
Familial Mediterranean fever is a hereditary inflammatory disorder affecting groups of patients originating from around the Mediterranean sea (hence its name). It manifests as attacks of serositis involving the abdomen, chest, or joints, accompanied by fever and elevated acute phase reactants. Attacks subside spontaneously within one to three days, although severe pain leaves many patients bedridden during the attacks. The primary complication is

amyloidosis leading to chronic renal failure. Daily colchicine reduces the frequency and duration of attacks and prevents renal amyloidosis.

The exact mechanism of colchicine action is not fully understood. However, the chief mechanism of action of colchicine seems to be the inhibition of microtubule polymerisation. Microtubules are involved not only in cell division, but also in signal transduction, regulation of gene expression, migration, and secretion. Colchicine exerts marked effects on leukocytes, altering their adhesion, mobility, and cytokine production. These mechanisms explain most of the anti-inflammatory effects of colchicine, which give rise to several therapeutic uses.
The antimitotic effect of colchicine is most prominent on cells with a high rate of division, such as those of the gastrointestinal epithelium and hematopoietic cells.
In the literature, a large number of adverse effects as a result of colchicine treatment are reported. Gastrointestinal effects are most frequently mentioned. Other adverse effects concern the musculature, the nervous system, and a number of secretion processes. As microtubules are involved in multiple cellular processes, interfering with their function may have many effects, some beneficial but many adverse.

III.2 Pharmacokinetics

Absorption of colchicine was rapid in rats. Colchicine distributes into many tissues, but primarily into bile, liver, spleen, and kidney. Colchicine also shows a preferential concentration in leukocytes, which may explain its therapeutic effects. Colchicine levels in brain were very low and plasma protein binding was generally not extensive. In general colchicine is primarily excreted via the bile, whereas a minority is excreted via the urine. Since it was shown that in several models of experimental liver dysfunction colchicine pharmacokinetics were significantly impaired, this should be taken into account when using colchicine in patients with liver dysfunction. The multidrug resistance efflux transporter P-glycoprotein is involved in colchicine transport. In addition, cytochrome P450 3A4 is involved in the metabolism of colchicine.

III.3 Toxicology

Single and repeat-dose toxicity
Single-dose toxicity studies in various animal species demonstrated a wide range in the toxicity of colchicine. LD50 values ranged from 0.24 mg/kg in new-born rats and 0.5 mg/kg in guinea pigs up to 470 mg/kg in golden hamster.
In rats given intraperitoneal injections of colchicine five times per week, with a starting dose of 0.1 mg/kg/day, doubled each week, to a final level of 1.6 mg/kg/day in the fifth week, no effects were seen during the first two weeks. In the third week (daily dose 0.4 mg/kg) weight loss began, ascites appeared, and 5% of the animals died. Over half of the rats eventually developed ascites. In the next week (0.8 mg/kg/day) diarrhoea first became prominent and an additional 4% of the animals died. Intoxication was not marked until the last week when the rats became dishevelled, bloody staining of the nose appeared, diarrhoea became severe, and a few showed hind leg paralysis. On this dosage (1.6 mg/kg/day), 35% died after only three injections.

Twelve cats were injected intraperitoneally with colchicine five times per week. The original dose of 0.025 mg/kg/day was doubled each week to 0.2 mg/kg/day in the fourth week. Two cats died in the second week and two more in the third. The second week (daily dose 0.05 mg/kg) showed diminished food consumption, beginning weight loss, and lethargy. By the third week all cats had developed ascites and atrophy of the hind quarters. The atrophy was extreme, the leg muscles being converted into thin strands. Also, fat nephrosis, marked karyorrhexis of lymphoid structures, abnormalities in the gastrointestinal mucosa, and hypocellularity of the marrow were shown. Despite this, the animals were normally active, had negligible gastrointestinal effects and there were no other neuromuscular disturbances.
Adult male rabbits were divided in three groups. One group received subcutaneous injections of 1.5 mg/kg colchicine twice weekly for a period of 15 weeks. The second group received subcutaneous injections of 3 mg/kg colchicine twice weekly for a period of 15 weeks. The third group served as a control. The rabbits tolerated the large dose without any apparent signs of toxicity. Post mortem examination of the various organs revealed no pathological lesions with the exception of the testis. Colchicine was found to arrest spermatogenesis and to produce atrophy of the testis without affecting the general health of the adult rabbits.
In rats, colchicine was daily administered intraperitoneally at a dosage of 0.4 or 0.8 mg/kg. Animals given colchicine at a dosage of 0.8 mg/kg showed severe toxic effects. These included weight losses of up to 27% within 4 days, diarrhoea, weakness and paralysis. Animals treated at 0.4 mg/kg demonstrated only mild toxic effects or no effects at all. In some muscle cells from animals treated with 0.8 mg/kg, myofilaments were oriented perpendicularly or obliquely to the longitudinal axis of the muscle fibre. Also found in the sarcoplasm of colchicine-treated animals were complex spheromembranous bodies, which appeared to be derived from the sarcoplasmic reticulum, and enveloped mitochondria or other organelles.

Genotoxicity

In a bacterial mutagenicity test, colchicine showed no mutagenic effect in the *Escherichia coli* Sd-4 strain, but a slight mutagenic effect in the *E. coli* WP-14 strain. In the *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, colchicine tested with and without S9 microsomal activation mixture was negative for mutagenicity.
In Chinese hamster ovary cells with and without S9, colchicine without activation did induce chromosome aberrations, mainly of the simple type, in addition to polyploidy. In a human lymphocyte test system for induction of aneuploidy and polyploidy, as well as for spindle effects, colchicine at 0.010 µg/ml and higher induced hypoploid, hyperploid and polyploid cells dose dependently. Colchicine, in a wide range of doses (0.015-0.105 µg/ml), also induced c-mitotic effects (i.e. complete or incomplete inactivation of the spindle) and an increase of the mitotic index. A number of other papers describe tests that demonstrate that colchicine is capable of inducing aneuploidy and/or polyploidy in cultured mammalian cells from a variety of species.
The consequence of aneuploidy is not at all clear. Weaver et al. (2007) describe that aneuploidy acts both oncogenically and as a tumour suppressor, e.g. in chemically or genetically induced tumour formation, an increased rate of aneuploidy is a more effective inhibitor than initiator of tumorigenesis.
Colchicine injected intraperitoneally was found to produce bone-marrow depression and micronuclei at 1.25-5.0 mg/kg in mice. Colchicine induced micronuclei with very high specific

activity in the Syrian hamster embryo cells (140 micronuclei/µmole), and at low concentrations (10-8 to 10-6 M) a dose-response was observed. However, an in vivo rat micronucleus test, integrated in a 14-day subchronic toxicity study, colchicine at 0.06, 0.6, and 6.0 mg/kg did not induce micronuclei, whereas this was expected from genotoxicity results described in the literature. It is suggested that the wide dose interval may explain the negative result, as colchicine is active only over a narrow dose range. In addition, colchicine was dosed orally in this study, whereas the doses applied were determined from another study in which colchicine was dosed intraperitoneally.
Colchicine tested for mutagenicity in *Drosophila melanogaster* was negative and colchicine was considered positive in the comet assay.

Carcinogenicity
No preclinical data were found in the literature that suggest a carcinogenic effect of colchicine. However, some reports describe a tumour promoting action of colchicine. For instance, Berenblum and Armuth (1977) demonstrated that in mice colchicine injected five, nine or 24 hours before tumour initiation with urethane and skin applications of TPA (12-O-tetradecanoylphorbol-13-acetate) as tumour promotion led to a significant increase in skin tumour incidence in the nine-hour group, and an increase in the percentage malignancy in both the five and nine-hour groups. These times corresponded to the peak of metaphase arrest by colchicine.

Reproductive and developmental toxicity
Female fertility
In mice, colchicine treatment on eggs inhibited sperm penetration and interfered with the second meiotic division and normal cleavage. Chromosome counts of eggs at the first cleavage revealed heteroploidy. In rabbit eggs, chromosome scattering and inhibition of fertilisation were not observed. Colchicine administration in mice resulted in an increase in hyperploid oocytes, and intravenously administered colchicine (4.0 mg/kg) was found to inhibit ovulation in rabbits.
Rats treated with colchicine showed a number of changes in luteal cell cholesterol metabolism: namely a 60% decline in stored cholesterol, a three-fold rise in the activity of the cholesterol synthesizing enzyme HMG CoA reductase, and a three-fold rise in the capacity of the cells to incorporate precursor 14C-acetate into cholesterol.
In sheep with colchicine administered intravenously at a dose of 1 mg/kg close to day 10 of the cycle, secretory granules containing progesterone disappeared from the luteal cells, as were microtubules. The concentration of progesterone in peripheral plasma fell to 48% at four hours after treatment. Apparently, colchicine disrupts the microtubular system in the luteal cell and thereby inhibits the intracellular transport of secretory granules.

Spermatogenesis
In rats, colchicine given ≥1.4 mg/kg subcutaneously, spermatogonial mitoses were arrested in metaphase after 3.5 to 24 hours. Meiosis was apparently not affected at 4.5 mg/kg for at least 6 hours after treatment, but after 24 hours the meiotic figures were abnormal. Colchicine in high doses tended to loosen the spermatids and spermatozoa from the other layers of the seminiferous tubule.

Rabbits given subcutaneous injections of 1.5 and 3 mg/kg colchicine twice weekly for a period of 15 weeks showed arrest of spermatogenesis and atrophy of the testis without affecting the general health.
Sperm abnormalities were reported in mice after intraperitoneal doses of 0.5 and 1 mg/kg colchicine for five days.
Colchicine (0.05 µg in 0.5 ml normal saline) injected into the central area of the testis of rats resulted in arrest of germ cell mitoses and meioses and a rapid depletion of the microtubules normally found within the Sertoli cell. Sloughing of cells into the lumen of seminiferous tubules was the most prominent feature noted. The disruption of Sertoli microtubules was responsible for sloughing of Sertoli fragments and associated germ cells, and the cytoskeletal support of the Sertoli cell was dependent upon the integrity of Sertoli microtubules. Long-term sacrifice after colchicine treatment allowed the Sertoli cells to regain microtubules and long processes but not their typical configuration. Spermatogenesis remained severely impaired.

Teratology
Offspring from pregnant rats injected with 4 mg/kg colchicine on embryonic Days 18, 19, and 20 were found to have isocortical and hippocampal structures greatly reduced in mass when examined at birth. Cells with pyknotic nuclei were found in layers five, four, and three of the cerebral isocortex, the habenula, and anterior medial nuclei of the thalamus. Brains taken at postnatal days 22 and 132 were reduced in overall size, and had a 20-30% reduction of cells at the vertex of the neocortex with up to 50% reduction in the thickness of the corpus callosum. A decrease in activity, an increase in fearfulness and/or decreased tendency to explore, reduced error scores on the Hebb-Williams maze, poor performance on the Maier elevated maze, and a lessened sensitivity to sound-induced seizures were correlated with these anatomical changes.
Colchicine injected intravenously into pregnant hamsters on the eighth day of gestation at levels of 10 mg/ kg produced a foetal mortality of 50%. Gross congenital malformations, consisting of microphthalmia, anophthalmia, umbilical hernia, exencephaly, and skeletal anomalies are found in significant numbers.
Pregnant mice at different gestational stages, ranging from two to 14 days after mating, received colchicine by a single subcutaneous injection at dose levels of 0.5 to 2.5 mg/kg. Foetal abnormalities observed were exencephaly, open eye, cleft palate and other abnormalities. The placenta of the mouse seems to permit permeation of colchicine. The foetal malformation and death may be induced by mitosis-arresting activity of colchicine on developing embryonic tissues.

Lactation
Colchicine is excreted into milk in goats and sheep.

III.4 Ecotoxicity /environmental risk assessment

Since Colchicine DMB is intended as a substitution for already marketed products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

The submission is intended for well-established use. As such, the MAH has not provided additional non-clinical studies and further studies are not required. An overview based on literature review is, thus, appropriate. The effects of colchicine are well known, and the literature on pharmacology, pharmacokinetics and toxicology has been adequately reviewed in the MAH's non-clinical overview.

IV. CLINICAL ASPECTS

IV.1 Introduction

As Colchicine DMB is intended as a well-established use medicinal product, the MAH has submitted a literature review encompassing the pharmacokinetics, where pharmacokinetic data of Colchicine DMB was bridged to studies using colchicine formulations and the Food and Drug Administration (FDA) registered product Colcrys (Takeda Pharmaceuticals America Inc.) 0.6 mg tablets, which has been registered since 1961. Pharmacodynamics, clinical efficacy and safety have also been linked to clinical studies and are considered to be adequate.

IV.2 Pharmacokinetics

The pharmacokinetics of the proposed products were bridged to studies retrieved from the published literature, the ClinicalTrials.gov website and the FDA summary reports for Colcrys particularly. The majority referenced studies used colchicine formulations available in Europe and the FDA approved Colcrys tablets. Further, the colchicine 0.5 mg tablets have been approved since 1998 and there is broad experience with these tablets. The SmPC is in accordance with the available information in the literature.

As the MAH refers to many clinical studies that have been conducted with the FDA approved Colcrys tablets, the company has compared the composition of the Colchicine Tiofarma tablets and Colcrys tablets. Both tablets have a similar composition and contain the same excipients, except for an extra binder/disintegrant (i.e. pre-gelatinised starch) in Colcrys tablets. Furthermore, Colcrys tablets are coated, whereas Colchicine DMB tablets are uncoated to avoid the risk of colorant induced allergic reactions.

<u>Biowaiver</u>
Comparative dissolution data have been submitted to support the biowaiver for the additional strength 1 mg tablet and justify bridging of Colchicine DMB 0.5 mg and 1 mg tablets to the pharmacokinetics data of colchicine formulations in the public literature and on Colcrys tablets. The two strengths of the proposed medicinal product showed dissolution similarity as both dissolved more than 85% within 15 minutes in water and three media with different pH

(i.e. pH 1.2, 4.5 and 6.8). The colchicine dissolution profiles of Colchicine DMB 0.5 and 1 mg tablets also demonstrated similarity with Colcrys 0,6 mg tablets.

Overall, the application contains an adequate review of published pharmacokinetics data. The bridging of the Colchicine DMB 0.5 and 1 mg tablet to the pharmacokinetics data described in literature and on Colcrys tablets has been sufficiently justified. In conclusion, the biowaiver between Colchicine DMB 0.5 mg and 1 mg tablets was approved based on comparable dissolution between both strengths.

IV.3 Pharmacodynamics

The major pharmacological action of colchicine is its ability to bind to tubulin dimers. Colchicine binds in an equimolar and poorly reversible manner to tubulin, forming a tubulin-colchicine complex in cells. It prevents the polymerisation of microtubules by binding their protein subunits and preventing conglomeration. By disrupting the cytoskeleton, it inhibits many signalling pathways and cellular events such as chemotaxis and phagocytosis, which explains most of the anti-inflammatory properties of this molecule. Colchicine has also marked effects on leukocyte function, preventing diapedesis, mobilisation, lysosomal degranulation, and chemotaxis.

IV.4 Clinical efficacy

Both colchicine 0.5 or 0.6 mg were used in the various randomised trials from the literature. Due to the availability of different dose strengths across regions, 0.6 mg or multiples thereof are usually employed in the North America, while 0.5 mg or multiples thereof are commonly employed in Europe.

Treatment of acute gout flares: randomised trial data

Pain and swelling usually abate within 12-24 hours of starting colchicine therapy, and symptoms have usually disappeared after 48 to 72 hours. Less than 5% of patients fail to obtain relief.

Two placebo-controlled randomised trials were retrieved from the literature.

The first study was the AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study. This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study to compare colchicine 1.2 mg, followed by 0.6 mg in one hour (“low dose”; 1.8 mg in total; n = 74) with colchicine 1.2 mg, followed by 0.6 mg hourly for six hours (“high dose”; 4.8 mg in total; n = 52) and placebo (n = 59) for treatment of acute gout flares, in male and postmenopausal female patients, 18 years of age, with a confirmed past diagnosis of gout (according to the American College of Rheumatology classification criteria) and having had two gout flares within the prior 12 months (Study MPC 004-06-3001; see also Terkeltaub et al., 2010). The primary endpoint was proportion of responders defined as having greater than 50% pain reduction at 24 hours without the use of rescue medications.

Both colchicine regimens (low-dose and high-dose) were shown to be significantly more effective than placebo, with 37.8% responders in the low-dose group, 32.7% responders in the high-dose group, and 15.5% responders in the placebo group (p = 0.005 and p = 0.034, respectively, versus placebo). Compared with placebo, the proportion of patients using rescue medication within the first 24 hours after intake of study medication was statistically significantly lower with low-dose colchicine (p = 0.027) and numerically lower although not statistically significant with high-dose colchicine (p = 0.103). The authors concluded that low-dose colchicine yielded early gout flare efficacy comparable to that with high-dose colchicine, and with a safety profile similar to that of placebo.

Of important note, 76.7% of participants receiving high-dose colchicine developed all three of the side effects of nausea, vomiting and diarrhoea, of which 19.2% had severe intensity diarrhoea. These side effects of nausea, vomiting and diarrhoea were considerably less common in the low-dose group with respective frequencies of 23.0%, 4.1%, and 25.7%, with none having severe intensity diarrhoea. The side effect profile for the placebo group was similar with the exception of a lower nausea frequency of 13.6%

The proof of concept has been demonstrated in the AGREE trial. Notably, the low dose (1.8 mg) was similarly effective as the high dose (4.8 mg), and better tolerated. Because of this study, the maximum recommended total daily dose in flares was reduced to 1.5 mg daily in the SmPC, after a starting dose of 1 mg.

The second study was a double-blind placebo-controlled study to compare colchicine 1 mg followed by 0.5 mg every two hours until complete response or toxicity occurred (n = 22), versus placebo (n = 21) in male and female patients, ≥18 years of age, with proven acute gout, confirmed by joint aspiration and the demonstration of negatively birefringent needle-shaped crystals (Ahern et al., 1987). Patients in the colchicine treatment group received a mean dose of 6.7 mg colchicine. A significantly greater proportion of the colchicine-treated patients responded within 48 hours with respect to the clinical and pain score (64 and 73% for clinical and pain score) compared with placebo (23 and 36% for the clinical and pain score, p<0.05). A significantly greater proportion of the colchicine-treated patients responded also earlier than the placebo group. The pain scores showed significant difference between colchicine and placebo after 18 hours, the clinical scored became significantly different after 30 hours.
The proof of concept has been demonstrated in this study. Due to the titration design and the small scale, it is difficult to establish the optimal dose from this study.

<u>Prevention of gout flares</u>
Low-dose colchicine has long been considered the mainstay of prophylaxis for acute gout flare, and clinical studies have reported significant reductions in flares when colchicine was administered in conjunction with allopurinol (p = 0.008) (Borstad et al., 2004) or probenecid (p<0.05) (Paulus et al., 1974) compared with either urate lowering therapy alone (see details below). The dosage regimens in these studies were allopurinol with or without 0.6 mg colchicine twice daily or placebo and 500 mg probenecid three times a day or with 500 mg probenecid plus 0.5 mg colchicine three times a day for six months.

The study reported by Paulus et al. (1974) was a six-month double-blind placebo-controlled study in patients started on urate-lowering therapy with probenecid. The study enrolled male patients with confirmed gout based (a serum uric acid level greater than 7.5 mg/dL) and a history of typical acute arthritis that responded promptly to treatment with colchicine. Patients were treated with 500 mg probenecid three times a day or with 500 mg probenecid plus 0.5 mg colchicine three times a day for six months. Patients were randomised to receive either colchicine 0.5 mg/probenecid (n = 20) or placebo/probenecid (n = 18) three times daily. Patients in the colchicine/probenecid group had a significantly lower rate of gout flares per month than patients receiving placebo (0.19 vs. 0.48, p<0.05). The authors concluded that treatment with 1.5 mg of colchicine in divided daily doses significantly decreases the frequency of attacks of acute gout in patients whose hyperuricemia has been satisfactorily controlled by probenecid.

The study by Borstad et al. (2004) was a double-blind placebo-controlled study of colchicine to determine if colchicine administration during initiation of allopurinol therapy for chronic gouty arthritis reduces the frequency and/or severity of acute gout flares in patients with crystal-proven gouty arthritis. Allopurinol was initiated at 100 mg orally per day. The dose was increased in 100 mg increments every two to three weeks until a serum urate level of <6.5 mg/dL was attained. Patients starting allopurinol were randomised to receive either 0.6 mg colchicine orally (n = 21) or placebo (n = 22). Subjects treated with colchicine has less total flares (0.52 vs. 2.91, p = 0.008), fewer flares from zero to three months (0.57 vs. 1.91, p=0.022), and fewer flares from three to six months (0 vs. 1.05, p = 0.003). Acute gout flares occurred in 33% of the colchicine patients and 77% of the placebo patients (p = 0.008). Multiple gout flares occurred in 14% of the colchicine patients vs. 63% of the placebo patients (p = 0.004). Severity of acute gout flares measured subjectively by the visual analogue scale averaged 3.64 in the colchicine group vs. 5.08 in the placebo group (p=0.018). The average length of acute gout flares did not vary significantly between the groups. There were seven withdrawals, three in the colchicine group and four in the placebo group. The authors concluded that colchicine prophylaxis during initiation of allopurinol for chronic gouty arthritis reduces the frequency and severity of acute flares, and reduces the likelihood of recurrent flares. The EULAR guidelines (Richette P, et al. 2016) for gout recommend that prophylaxis be administered during the early months of urate lowering therapy to reduce the risk of flares. In conclusion, colchicine is clearly effective in preventing gout flares at the introduction of urate lowering therapy in gout.

<u>Familial mediterranean fever (FMF)</u>

The study reported by Dinarello et al. (1974) was a randomised, double-blind, placebo-controlled study in 11 patients with long standing FMF who were treated with colchicine (0.6 mg tablets, three times daily) or placebo in random order for 28 days (one course). If no attacks occurred during the 28-day period, the next course was started. When an attack occurred, the course was stopped. After recovery (usually after several days), the patient began the next course. During 60 courses of placebo, 38 attacks occurred (63%), compared with seven attacks during 60 courses of colchicine (12%; p<0.001). The study was discontinued after six of 11 enrolled patients had completed the study (after 11-month study period), when a planned interim analysis was interpreted to indicate a clear benefit with the colchicine

treatment. Attacks were rated as severe for 17 of 34 attacks on placebo with severity information available, compared with one of seven attacks that occurred during colchicine therapy.

The study reported by Goldstein and Schwabe (1974) was a double-blind, crossover study in ten patients with a high frequency of FMF attacks who were treated -in random order- with colchicine (0.6 mg; one tablet three times a day) or placebo for three months. On placebo-therapy, 59 attacks occurred in nine of the ten patients over three months, compared with five attacks in two of the ten patients on colchicine over three months ($p<0.002$). Overall, 80% of the patients had no attacks during colchicine treatment, whereas 10% of patients were free of symptoms on the placebo regimen.

The third study was a double-blind crossover study reported by Zemer et al. (1974) in 22 patients who received -in random order- two-month treatment with 0.5 mg colchicine b.i.d. or placebo. During the first two months of the study, the colchicine group had significantly fewer attacks (mean 1.15 per patient, n = 10) than the placebo group (mean 5.25 per patient, n = 10) ($p<0.01$). The patients who completed the crossover study (n = 13) had significant fewer attacks on colchicine than on placebo ($p<0.01$). The mean decrease in the number of attacks on colchicine was 3.85. Eleven patients had fewer attacks during the two months on colchicine than on placebo; one patient had more attacks and one patient had no change.

<u>FMF dosing recommendations</u>
Treatment recommendations for use of colchicine in children and adolescents with FMF were published in 2007 (Kallinich et al., 2007). The continuous use of colchicine for prophylaxis of attacks and prevention of amyloidosis is recommended for children with FMF. Treatment should be started as soon as the diagnosis has been established and continued for life. Colchicine is also recommended for the treatment of amyloidosis. The dosage should be adjusted for age and renal function, as follows:

- The recommended starting dose is 0.5 mg/day (for children <5 years of age), 1.0 mg/day (for children 5-10 years of age), or 1.5 mg/day (for children >10 years of age). The dosage should be increased in a stepwise fashion (e.g., 0.25 mg/step) up to a maximum of 2.0 mg/day to control disease in patients who do not clinically respond to the standard dosage.
- Higher colchicine doses (up to 2 mg/day) should be applied in high-risk patients (e.g., after kidney transplantation, patients with amyloidosis), independent of the dose needed for control of clinical symptoms.

In a more recent publication from a group of international clinical experts it was concluded that the recommended dose for adults with FMF is 1 – 3 mg/day and for children before puberty up to 2 mg/day (Hentgen et al., 2013).

Although the total number of patients enrolled in the randomised studies on FMF was small (n = 48 in total), the treatment effect observed was sufficient to allow the three trials to demonstrate evidence of efficacy in the reduction in the number of acute attacks experienced by the patients.

Not mentioned by the MAH is that colchicine also prevents amyloidosis and proteinuria secondary to renal amyloidosis. E.g., in a cohort of 980 patients, 30% of adult patients without colchicine treatment –since it was not available at that time-developed proteinuria, whereas only 0.4% of patients taking colchicine showed kidney involvement during an observation period up to 11 years. The cumulative rate of proteinuria in this study was 1.7% (90 % CI 0.0-11.3%) in the treatment compliant patients and 48.9% (18.8 -79.0 %) in the non-compliant patients (P< 0.0001) (Zemer *et al.,* 1986).

IV.5 Clinical safety

The following sections summarize safety data from clinical studies. Only acute (short-term) studies were retrieved from the literature. For long-term safety, the worldwide marketing experience with colchicine is utilized.

Safety data from clinical studies in patients with gout

Adverse events reported by more than one patient overall for the treatment of acute gout in Study MPC 004-06-3001 (AGREE Study, Terkeltaub *et al*., 2010) are summarised in table 1. Patients in this study were treated with low-dose (1.8 mg colchicine over two hours), high-dose (4.8 mg colchicine over six hours) or placebo.

Table 1: Adverse events reported by two or more patients (Study MPC 004-06-3001)

	Low Dose (N=74)		High Dose (N=52)		Placebo* (N=58)	
Any adverse event	27	(36.5%)	40	(76.9%)	16	(27.6%)
Gastrointestinal disorders						
Diarrhea	17	(23.0%)	40	(76.9%)	8	(13.8%)
Nausea	3	(4.1%)	9	(17.3%)	3	(5.2%)
Abdominal Pain	-		1	(1.9%)	1	(1.7%)
Abdominal Discomfort	-		-		2	(3.4%)
General disorders						
Vomiting	-		9	(17.3%)	-	
Fatigue	1	(1.4%)	2	(3.8%)	1	(1.7%)
Metabolism and nutrition disorders						
Gout	3	(4.1%)	-		1	(1.7%)
Nervous system disorders						
Headache	1	(1.4%)	1	(1.9%)	2	(3.4%)
Respiratory, thoracic and mediastinal disorders						
Pharyngolaryngeal pain	2	(2.7%)	1	(1.9%)	-	
Skin and subcutaneous tissue disorders						
Rash	1	(1.4%)	-		1	(1.7%)
Vascular disorders						
Hypertension	-		1	(1.9%)	1	(1.7%)

*N=59 in the results that were posted by MPC on the ClinicalTrials.gov website (http://clinicaltrial.gov) and in the publication by Terkeltaub et al., 2010. However, N=58 was used by the FDA in their summary report for Colcrys Application 22-351. The latter approach is considered more conservative since it yields higher incidence rates and was therefore used for this table.

There was no effect on the corrected QT (QTc) interval or any other electrocardiogram (ECG) parameter with therapeutic doses of colchicine, as assessed in two clinical pharmacology studies.

Serious adverse events (SAE) and lethal cases

Report of serious events or deaths related to colchicine therapy in the published medical literature were primarily found in articles discussing the toxicity of colchicine, and in case reports of acute or chronic overdose. Approximately one-third of the fatalities associated with colchicine therapy in the post marketing adverse event World Health Organization (WHO) and FDA databases was associated with overdose. Of the fatalities not associated with an overdose, approximately half of the cases reported clarithromycin as a co-suspect, concomitant or interacting drug.

Special populations

The adverse event profile was comparable in young (18 - 30 years of age) and elderly (>60 years old) healthy subjects who received a single 0.6 mg dose of colchicine (Study MPC-004-09-1027), with the exception of increased blood pressure that was more often reported by elderly than by young subjects.

A study performed by Berkun et al (2012) to describe the pharmacokinetics of colchicine in paediatric patients (2 – 16 years of age) demonstrated that the safety profile in children as young as two years of age was comparable to that seen in older children and adults.

FMF is predominant among persons with non-Ashkenazi Jews, Arabic, Turkish or Armenian descent. Since treatment often starts at a young age, safety data collected in this indication also included the paediatric population. There do not appear any specific safety issues or concerns associated with paediatric use.

Drug interactions

Fatal and non-fatal cases of colchicine toxicity have also been reported in the literature with concomitant use of clarithromycin or other CYP3A4 and P-gp inhibitors, such as cyclosporine, erythromycin, and calcium channel antagonists such as verapamil and diltiazem. Other examples of P-gp and strong CYP3A4 inhibitors include telithromycin, ketoconazole, itraconazole, HIV protease inhibitors, and nefazodone.

Case reports have been published that link colchicine use to myotoxicity or potentiation of statin-induced (i.e., fluvastatin, lovastatin, and pravastatin) myopathy. The results from Study MPC-004-08-1019 only showed a modest (20%) increase in colchicine C_{max} and AUC with concomitant use of atorvastatin. It is therefore believed that the interaction between colchicine and statins is not solely pharmacokinetic but may also involve disruption of the cytoskeleton, which could be attributed to either drug. It cannot be excluded that fibrates, cyclosporin or digoxine increase the risk of myopathy or rhabdomyolyse when combined with colchicine.

Overdose

Colchicine has a narrow therapeutic index. Colchicine's toxicity is an extension of its mechanism of action – binding to tubulin and disrupting the microtubular network eventually leading to multi-organ dysfunction and failure. Medical outcome of cases of colchicine exposure from the Texas Poison Centre Network Data (years 2000 to 2005) were reported as no effect (24%), minor effect (20%), moderate effect (15%), and major effect (3%). The most common clinical findings included vomiting (20%), diarrhoea (17%), and abdominal pain (7%). The majority of cases of exposure produced no significant effects, and fatality was uncommon. If however the overdose is significant enough, death may result from rapidly progressive multi-organ failure and sepsis. Delayed presentation, pre-existing renal or liver impairment are associated with poor prognosis. Treatment of overdose symptoms should begin with activated charcoal and/or gastric lavage. Otherwise, treatment is symptomatic and supportive. No specific antidote is known. Colchicine is not effectively removed by haemodialysis. Although colchicine poisoning is relatively uncommon, it is imperative to recognize its features as it is associated with a high mortality rate when missed (Finkelstein et al., 2010).

Post-authorisation database

The most frequently reported adverse events are gastrointestinal disorders (i.e., diarrhoea, nausea and vomiting, abdominal pain and cramping). Gastrointestinal events occur

approximately eight to 12 hours after oral administration in 80% of patients, especially when maximal doses are used (Levy et al., 1991). In the FDA post marketing databases, 340 of 751 (45%) reports were for gastrointestinal adverse events, with diarrhoea being the most common, for the period from 1969 to 30 June 2007. For the period from 1968 to March 2006, 46% (633/1380) of reports in the WHO post marketing database were related to gastrointestinal events (Colcrys Application 22-352). Prolonged administration of colchicine may further be associated with malabsorption and intestinal enzyme activity defects. The malabsorptive syndrome is reversible and is related to a disruption of intestinal mucosal function.

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 Colchicine DMB.

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

Important identified risks	• Bone marrow depression with agranulocytosis and aplastic anaemia • Myopathy • Rhabdomyolysis
Important potential risks	• Potential for medication errors • Potential for harm of overdose
Missing information	• Use in pregnancy • Use during lactation • Use in men with child wish

The member states 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

This mutual recognition procedure concerns a well-established use application for Colchicine DMB. For this authorisation, reference is made to literature. No new clinical studies were conducted. Risk management is adequately addressed. Altogether it is considered that efficacy of colchicine in the treatment of acute gout, the prophylaxis of a gout attack during initiation of urate-lowering therapy and FMF has been established as the majority of studies in subjects showed statistically significant and clinically relevant results. Finally, it is considered that the safety issues that are identified are adequately addressed in the SmPC.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of two rounds of questions with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Colchicine DMB 0.5 mg and 1 mg tablets have a proven chemical-pharmaceutical quality. Colchicine DMB has an adequate efficacy and safety profile and is considered widely established.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Colchicine DMB with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 4 March 2021.

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

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