

Public Assessment Report

Scientific discussion

Colchicine Tiofarma 1.0 mg, tablets

(colchicine)

NL License RVG: 115060

Date: 16 April 2018

This module reflects the scientific discussion for the approval of Colchicine Tiofarma 1.0 mg, tablets. The procedure was finalised on 6 November 2015. 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 |
| FDA | Food and Drug Administration (USA) |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |
| WHO | World Health Organization |

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Colchicine Tiofarma 1.0 mg, tablets, from Tiofarma B.V.

The product is indicated for:

Adults

- Colchicine is indicated for the treatment of acute gout when Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are contraindicated or are not tolerated by the patient.
- Colchicine is indicated for the prophylaxis of a gout attack during initiation of urate-lowering therapy when NSAIDs are contraindicated or are not tolerated by the patient

Adults and paediatric patients

- Colchicine is indicated in Familial Mediterranean Fever (FMF) for prophylaxis of attacks and prevention of amyloidosis.

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

This national procedure concerns a line extension to the existing marketing authorisation of Colchicine Tiofarma 0.5 mg, tablets (NL license RVG 21347) which was approved for marketing in The Netherlands on 25 December 1998 and last renewed on 28 December 2013. In addition, this procedure concerns an extension of the indications with chronic treatment of FMF, in both children and adults.

This is a bibliographical application based on 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 the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. "Medicinal use" does not exclusively mean "use as an authorised medicinal product", so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Colchicine Tiofarma 1 mg is a off-white, oval tablet with the inscription "C1C" on one side. Each tablet contains 1 mg of colchicine.

The tablets are packed in PVC/Alu blisters and/or polypropylene containers with a closure.

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

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. The

active substance is very soluble in water, rapidly recrystallizing from concentrated solutions as the sesquihydrate; freely soluble in alcohol and chloroform and practically insoluble in cyclohexane. 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 European Pharmacopoeia.

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., 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 this specification have been provided for two production scaled 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 1 mg product was developed based on the already marketed Colchicine 0.5 mg tablet. 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

The manufacturing process has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques (wet granulation) and the process consists of the following steps: weighing, dissolution, mixing, drying, sieving, tableting and packaging. Process validation data on the product have been presented for full-scale production batches in accordance with the relevant European guidelines. Based on these data it can be concluded that the manufacturing process of the tablets is controlled and consistently demonstrates compliance to the finished product specifications.

Control of excipients

The excipients comply with the Ph. Eur. 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 (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. The release and shelf-life requirements/ limits of both strengths are identical and acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical

data from 3 commercial scaled batches of both strengths 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 3 full scaled batches of both strengths stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were stored in the proposed packaging. 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 (OOS results), but stayed within specification under long term conditions up to 36 months. All other parameters showed no up or downward trends and stayed within limits. A photostability study was performed on the tablets. It is evident from the results of the photostability study that the tablets are sensitive to light. Light sensitivity of colchicine is also confirmed by the Ph. Eur. However, when packed in both primary and secondary packaging as described above, all parameters tested were found to be within the specified limits.

Based on the provided information the proposed shelf-life of 36 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 6 months.

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

The used lactose monohydrate is of animal origin but is not considered to be any risk of Transmissible Spongiform Encephalopathy (TSE) contamination as it complies with the current TSE Directive.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Colchicine Tiofarma 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 Ecotoxicity/environmental risk assessment (ERA)

Since Colchicine Tiofarma is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The application is 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 non-clinical overview refers to 126 publications up to year 2010. The effects of colchicine are well known, and the literature on the acute and chronic toxicity, genotoxicity, carcinogenicity and reproductive toxicity has been adequately reviewed in the applicant's non-clinical overview.

IV. CLINICAL ASPECTS

IV.1 Introduction

Colchicine is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of colchicine. The MAH submitted a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

IV.2 Pharmacokinetics

The pharmacokinetics of the proposed products were bridged to studies retrieved from the published literature, the ClinicalTrials.gov website and the summary reports of the Food and Drug Administration (FDA) in the United States for Colcrys (Application Number 22-351, 22-352 and 22-353) particularly. The majority referenced studies used colchicine formulations available in Europe and the FDA approved Colcrys tablets. Furthermore, the colchicine 0.5 mg tablets have been approved since 1998 and there is broad experience with these tablets. The SmPC in accordance with the available information in the literature.

As the company 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 Tiofarma tablets are uncoated. Tiofarma had chosen the use of uncoated tablets to avoid the risk of colorant induced allergic reactions.

Comparative dissolution data have been submitted to support the biowaiver for the additional strength 1mg tablet and justify bridging of Colchicine Tiofarma 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 Tiofarma 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 Tiofarma 0.5 and 1 mg tablet to the pharmacokinetics data described in literature and on Colcrys tablets has been sufficiently justified.

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, mobilization, lysosomal degranulation, and chemotaxis.

IV.4 Clinical efficacy

Both colchicine 0.5 or 0.6 mg were used in the diverse randomised trials from the literature. Due to the availability of different dose strengths across regions, 0.6 mg or multiples thereof is usually employed in the North America, while 0.5 mg or multiples thereof is 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 1 hour ("low dose"; 1.8 mg in total; n=74) with colchicine 1.2 mg, followed by 0.6 mg hourly for 6 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 2 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 second study was a double-blind placebo-controlled study to compare colchicine 1 mg followed by 0.5 mg every 2 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 score became significantly different after 30 hours.

Prevention of Gout Flares

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 ($p<0.05$) 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 b.i.d. or placebo and 500 mg probenecid 3 times a day or with 500 mg probenecid plus 0.5 mg colchicine 3 times a day for 6 months.

The study reported by Paulus et al. (1974) was a 6-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 3 times a day or with 500 mg probenecid plus 0.5 mg colchicine 3 times a day for 6 months. Patients were randomised to receive either colchicine 0.5 mg/probenecid ($n=20$) or placebo/probenecid ($n=18$) 3 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 per os (p.o.) per day. The dose was increased in 100 mg increments every 2 to 3 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 b.i.d. ($n=21$) or placebo ($n=22$). Subjects treated with colchicine has less total flares (0.52 vs. 2.91, $p=0.008$), fewer flares from 0 to 3 months (0.57 vs. 1.91, $p=0.022$), and fewer flares from 3 to 6 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 7 withdrawals, 3 in the colchicine group and 4 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 for gout recommend that prophylaxis be administered during the early months of urate lowering therapy to reduce the risk of flares.

Familial Mediterranean Fever (FMF)

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, 3 times daily) or placebo in random order for 28 days (1 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 7 attacks during 60 courses of colchicine (12%; $p < 0.001$). The study was discontinued after 6 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 1 of 7 attacks that occurred during colchicine therapy.

The study reported by Goldstein and Schwabe (1974) was a double-blind, crossover study in 10 patients with a high frequency of FMF attacks who were treated -in random order- with colchicine (0.6 mg; 1 tablet 3 times a day) or placebo for 3 months. On placebo-therapy, 59 attacks occurred in 9 of the 10 patients over 3 months, compared with 5 attacks in 2 of the 10 patients on colchicine over 3 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- 2-month treatment with 0.5 mg colchicine b.i.d. or placebo. During the first 2 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 2 months on colchicine than on placebo; 1 patient had more attacks and 1 patient had no change.

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).

IV.5 Clinical safety

The following sections summarise safety data from clinical studies. Only acute (short-term) studies were retrieved from the literature. For long-term safety, Tiofarma is relying on the worldwide marketing experience.

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 2 hours), high-dose (4.8 mg colchicine over 6 hours) or placebo.

Table 1: Adverse events reported by 2 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://clinicaltrials.gov>) and in the publication by Terkeltaub et al., 2010. However, N=58 was used by the FDA in their summary report for Colcry 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 interval or any other electrocardiogram parameter with therapeutic doses of colchicine, as assessed in 2 clinical pharmacology studies.

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: age

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 2 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 (see Colchicine Public Assessment Report for paediatric studies).

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 (Section 2.5.3.3.1) 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 rhabdomyolysis when combined with colchicine.

Overdose

Colchicine has a narrow therapeutic index. High fatality rate was reported after acute ingestions exceeding 0.5 mg/kg. The lethal dose for adults is usually about 20 mg. 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 Center 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 recognise its features as it is associated with a high mortality rate when missed (Finkelstein et al., 2010).

Post-authorisation database

Safety data for colchicine 0.5 mg tablets received from world-wide sources during the period from 01 August 2007 up to and including 31 July 2010 were assessed by the MAH. The most frequently reported adverse events are gastrointestinal disorders (i.e., diarrhoea, nausea and vomiting, abdominal pain and cramping). Gastrointestinal events occur approximately 8 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 malabsorption syndrome is reversible and 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 Tiofarma.

- 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 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

Colchicine has been used and is registered for the requested indications for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of colchicine in the proposed indications can be considered well-established with demonstrated efficacy. The proposed dose for both indications is in line with current recommendations. On the basis thereof, the efficacy of colchicine Tiofarma 0.5 mg and 1.0 mg, tablets can be considered well-established and acceptable.

V. USER CONSULTATION

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Colchicine Tiofarma 1.0 mg, tablets has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the proposed indications as well as the proposed posology are in line with current colchicine use and recommendations in the RMS and CMS countries, in which colchicine has been registered for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of colchicine in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Colchicine Tiofarma was authorised in the Netherlands on 6 November 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|--|------------------------------|--------------------------|------------------------|-----------------------------------|
| <ul style="list-style-type: none"> Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites): <ul style="list-style-type: none"> The activities for which the manufacturer/importer is responsible include batch release The activities for which the manufacturer/importer is responsible do not include batch release Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: <ul style="list-style-type: none"> Secondary packaging site Primary packaging site Change to importer, batch release arrangements and quality control testing of the finished product; Replacement or addition of a site where batch control/testing takes place | No | 08-02-2016 | Approved | - |
| Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location [2x] | No | 19-07-2016 | Approved | - |
| <ul style="list-style-type: none"> Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites); The activities for which the manufacturer/importer is responsible include batch release Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) [2x] Change in the name and/or address of the marketing authorisation holder | No | 08-08-2016 | Approved | - |
| Extension of the shelf life of the finished product; As packaged for sale (supported by real time data) | No | 23-08-2016 | Approved | - |
| Change in the shelf-life or storage conditions of the finished product; Extension of the shelf life of the finished product; After first opening [2x] | No | 24-08-2016 | Approved | - |