IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Colchicine Halewood
Colchicine
PA22902/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Colchicine Halewood 500 microgram Tablets, from Halewood Chemicals (Ireland) Ltd, on 11th April 2025 for the following indications:

Adults
Treatment of acute gout.
Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs.

Paediatric population
Colchicine is indicated in Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis.

The application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC, referred to as a bibliographic application based on the well-established use of colchicine on the European market for at least ten years, with recognised efficacy and an acceptable safety profile. This means that that the Marketing Authorisation Holder (MAH) is not required to provide results of pre-clinical and clinical trials as the active substance is well known, as supported by bibliographic literature.

The prescription status is that this medicine is subject to a medical prescription that may not be renewed. As colchicine is categorised as a narrow therapeutic index medicine, Colchicine Halewood 500 microgram Tablets are not regarded as an interchangeable medicine by the HPRA.

The applicant obtained scientific advice from HPRA in 2017, regarding the submission of a well-established use application for Colchicine Halewood 500 microgram Tablets.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Colchicine Halewood
Name(s) of the active substance(s) (INN)	Colchicine
Pharmacotherapeutic classification (ATC Code)	M04AC01
Pharmaceutical form and strength(s)	Tablet, 500 microgram(s)
Marketing Authorisation Number(s) in Ireland (PA)	PA22902/002/001
Marketing Authorisation Holder	Halewood Chemicals (Ireland) Limited North Point Business Park Old Mallow Road Cork T23 AT2P Ireland

II. QUALITY ASPECTS

II.1. Introduction

This application is for Colchicine Halewood 500 microgram(s) Tablets.

II.2 Drug substance

The active substance is Colchicine an established active substance described in the European/British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each tablet contains 500 micrograms of colchicine.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Colchicine Halewood 500 microgram Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for many years. Preclinical data have been superseded by clinical experience. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Colchicine are well known. As Colchicine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings are adequately mentioned in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Colchicine is a well-known active substance with established efficacy and tolerability. The MAH submitted an adequate bibliographic literature review of the clinical pharmacology, efficacy and safety of colchicine.

IV.2 Pharmacokinetics

The application contains an adequate bibliographic review of the published pharmacokinetics data for colchicine.

Colchicine is rapidly and almost completely absorbed after oral administration. Maximum plasma concentrations are met usually after 30 to 120 minutes. The terminal half-life is 3 to 10 hours. Plasma protein binding is approximately 30%. Colchicine is partially metabolised in the liver and then in part via the bile. It accumulates in leucocytes. Colchicine is largely excreted (80%) in unchanged form and as metabolites in the faeces; 10-20% is excreted in the urine.

Clearance of colchicine is decreased in patients with impaired renal function. Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis. There is a lack of pharmacokinetic data in children.

As a well-established use application, under Article 10 (1) of Directive 2201/83/EC, a bioequivalence study is not required.

In a previous application (UK/H/5392/01/DC) the applicant was requested to submit one bioequivalence study comparing the pharmacokinetic profile of the Test product Colchicine 500 microgram Tablets (Halewood) with the pharmacokinetic profile of a Reference product, Colchicine 500 microgram Tablets (Wockhardt, UK), the results of which are presented here for completeness.

Colchicine is categorised as a narrow therapeutic index medicine. According to the CHMPS's Colchicine table 0.5 mg and 1 mg product-specific bioequivalence guidance, (EMA/CHMP/35552/2019) the accepted 90% confidence interval range for bioequivalence is 80.00% to 125.00% for Cmax and 90.00% to 111.11% for AUC0-t values.

A single-dose, two-treatment, two-period, balanced randomised, cross-over, 14 days washout, clinical bioequivalence study was carried out between the Test and Reference in 28 healthy male volunteers under fasting conditions.

The HPRA was assured that GCP standards were adhered to in the study conducted.

Peak plasma concentrations occurred at about 1.5 hours after dosing for both Test and
Reference products, with Cmax values of 3.013(±0.369) ng/ml and 2.923(±0.432) ng/ml respectively. The adjusted geometric mean ratio between treatments for Cmax was 1.038 with a 90% confidence interval of 0.97 -1.11, showing bioequivalence for Cmax.

The mean values for the AUC0-t were 6.924 (±5.672) h*ng/ml for the Test product and 7.607(±6.861) h*ng/ml for the Reference product. The adjusted geometric mean ratio for AUC0-t between treatments of 0.932, with a 90% confidence interval of 0.75 - 1.17, did not show bioequivalence for AUC0-t.

Dissolution testing was conducted in accordance with the BP Monograph for Colchicine Tablets in place at the time. The proposed medicinal product showed a satisfactory dissolution profile as more than 85% dissolved within 15 minutes in water and in three media with different pH (i.e. pH 1.2, 4.5 and 6.8).

There was no difference in the safety profiles between Test and Reference products.

The applicant, on investigation, identified sample size, bioanalytical methodology issues and potential reduced potency in the Test product that was evaluated in the study as possible reasons for the lack of bioquivalence for AUC0-t in that study. Also, the absorption characteristics of colchicine produced a very high intra-subject variability (>40%), drugs with a co-efficient of variation >30% understood to be "highly variable".

In terms of therapeutic equivalence, the similar point estimate and the 90% confident intervals inside the 80.00-125.00% range for Test and Reference indicated a difference in exposure between the formulations of less than 20%. This is not expected to be clinically relevant in terms of the desired pharmacological effects; the posology for colchicine, in the indications applied for, allows for variation of dose depending on clinical response, with discontinuation advised if any signs of toxicity arise (nausea, vomiting, abdominal pain, diarrhoea). Also, as a narrow therapeutic index product, the applicant's colchicine medicinal product is not regarded as interchangeable by HPRA.

In the current bibliographic application, the MAH provided an updated expert review of the current literature and evidence of current clinical use of colchicine. The MAH has adequately justified the bio-inequivalence seen in the study described above, in the context of the new bibliographic application. The MAH has satisfactorily bridged their colchicine medicinal product to the current literature from an efficacy and safety perspective

IV.3 Pharmacodynamics

The application contains an adequate bibliographic review of published pharmacodynamics data for colchicine.

The mechanism of action of colchicine in the treatment of gout is not clearly understood. Colchicine is considered to act against the inflammatory response to urate crystals, by possibly inhibiting the migration of granulocytes into the inflamed area. Other properties of colchicine, such as interaction with the microtubules, could also contribute to the operation. Onset of action is approximately 12 hours after oral administration and is maximal after 1 to 2 days.

Colchicine prophylaxis (0.6 mg twice daily) during initiation of allopurinol for chronic gouty arthritis reduced the frequency and severity of acute flares, and reduced the likelihood of recurrent flares. Treatment may be continued for up to 6 months, based on clinical data. Prospective randomized controlled trials are needed to further evaluate flare prophylaxis for up to 6 months, after 6 months, and over time.

IV.4 Clinical Efficacy

In this bibliographic, well-established use application, the applicant has documented the effects of colchicine through reference to published studies. The bibliographic search supporting the expert clinical review submitted was conducted within the NLM PubMed® Medline and Embase® databases, as well as within the Cochrane Database of Systematic Reviews, standard medical texts, clinical practice guidelines and other general RCT internet searches.

<u>Acute Gout:</u>
Van Echteld et al. (Van Echteld 2014) reported a Cochrane meta-analysis of available
data in support of the use of colchicine for the treatment of acute gout. Of a total of 1035 articles from the standard databases (Medline, Embase, etc.), three studies were retrieved for full assessment (Ahern 1987, Schlesinger 2006, Terkeltaub 2010). Only the published RCT reports from Ahern and Terkeltaub fulfilled the search criteria for the Cochrane Review.

In the first double-blinded randomised, controlled trial, (Ahern 1987), 22 participants who were treated with high-dose colchicine (1 mg oral colchicine then 0.5 mg every two hours until there was either relief of pain or side effects from the drug) were compared with 21 participants treated with placebo, for acute gout attacks. All patients had the diagnosis of acute gout confirmed by joint aspiration and demonstration of negatively birefringent needle-shaped monosodium urate crystals under light microscopy. No NSAIDs were allowed for 48 hours before or during the study. Participants were assessed every six hours for 48 hours. Pain was measured on a 100-point visual analogue scale (VAS) and results were reported as proportion with 50% or greater improvement in pain from baseline at 12, 24, 36 and 48 hours, with mean pain scores at six-hourly intervals to 48 hours shown graphically. A compound clinical score comprised of pain, tenderness, redness and swelling (on a four-point scale,

0 to 3 score recorded for each symptom, maximum compound score of 12) was also recorded and presented as proportion with 50% or greater improvement in clinical score from baseline at 12, 24, 36 and 48 hours.
Two-thirds of patients receiving active treatment showed major clinical improvement (>50% improvement in objective manifestations) within 48 hours, compared to a third of patients receiving placebo.
Statistically significant differences in comparison with placebo were apparent 18 to 30 hours after starting treatment, with a 34% reduction in pain score and 30% reduction in clinical symptoms (such as tenderness on palpation, swelling and redness) for patients receiving colchicine.

In the second double blind, randomised, controlled trial (Terkeltaub 2010), the AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study, low- and high-dose colchicine were compared in 575 participants, who were included if they had a diagnosis of acute gout according to the ACR preliminary classification criteria. The high-dose prolonged colchicine regimen (4.8 mg total over 6 hours) was compared with a placebo and a low-dose abbreviated regimen (1.8 mg total over 1 hour, i.e. 1.2 mg followed by 0.6 mg in 1 hour).
Both colchicine regimens were significantly more effective than placebo, with 32.7% responders in the high-dose group, 37.8% responders in the low-dose group, and 15.5% responders in the placebo group (P = 0.034 and P = 0.005, respectively, versus placebo). The results at the primary 24-hour end-point demonstrate superior safety of low-dose colchicine, without loss of efficacy, relative to high-dose colchicine for early acute gout flare (self-administered within 12 hours of flare onset). The pharmacokinetic analysis performed in this study showed that the colchicine plasma concentration was decreased substantially from about 12 hours after administration in healthy volunteers.

In recent years numerous systematic reviews of the data conducted (Van Echteld 2014, Khanna 2014, Wechalekar 2014, Underwood 2015, Shekelle 2016, Engel 2017,Shekelle 2017).
are generally consistent in their conclusions, based on the limited body of available data relating to colchicine, that:

- High-level evidence supports use of colchicine as a first-line treatment for acute gout flares, recognising its ability to reduce the pain associated with the flare.
- Moderate-quality evidence shows that low-dose colchicine is as effective as higher doses.

Prophylaxis of gout

The first published study to consider the role of colchicine as prophylaxis for flare (Paulus 1974) investigated the serum urate-lowering effect of probenecid, as a means of monitoring compliance in a double-blind, parallel, placebo-controlled study. Fifty-one (51) male patients with gout were treated for six months, with the diagnosis of gout based on the presence of hyperuricemia (serum urate > 7.5 mg/100 ml) and a history of typical attacks of acute arthritis that responded promptly to intensive colchicine therapy.

Patients were randomised to probenecid with either 0.5 mg colchicine three times a day or placebo. Prophylactic probenecid-colchicine significantly reduced the gout flare rate versus probenecid- placebo (2.3 vs. 6 attacks per year of therapy, $p<0.05$).

In a double-blind, randomised, placebo-controlled trial (Borstad 2004) oral colchicine 0.6 mg (n=21) given once daily for up to six months was significantly more effective than placebo (n=22) at preventing gout flares (12 flares vs. 65 flares, respectively) in patients starting allopurinol therapy. Efficacy was seen in terms of the proportions of patients reporting acute (33% vs. 77%) and recurrent (14% vs. 63%) flares and mean flare severity (3.64 vs. 5.08). If colchicine was discontinued after eight weeks flare rates increased considerably (by up to 40%); if prophylaxis was maintained for six months, the flare rate remained low on discontinuation of colchicine.

One systematic review (Seth 2014) assessed these 2 trials and concluded that the data support the use of low-dose colchicine as prophylaxis against acute gout attacks, for use over at least six months, when initiating urate lowering therapy.

In an analysis of three other trials (Wortmann 2010) in which 0.6 mg colchicine dosed once or twice daily was administered as prophylaxis at the start of ULT, the overall finding was that gout flare frequency was lower when colchicine was part of the treatment regimen. When colchicine prophylaxis was discontinued after eight weeks, there was a marked increase in the frequency of gout flares; whereas no such increase was seen when colchicine prophylaxis was discontinued after six months.

Another systematic review (Latourte 2014) and one assessment of the evidence base (White 2014), identifying these 2 studies, and other analyses (Shekelle 2016, Engel 2017, Shekelle 2017) identify:

- high strength evidence supporting use of colchicine to reduce the risk of gout flares when starting ULT and
- moderate strength evidence indicating that longer courses (>eight weeks) are more effective that short-duration prophylaxis.

Familial Mediterranean Fever (FMF**)**

Dinarello et al. (1974) reported 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 over a 28-day course. If an attack occurred, the respective course of treatment was discontinued; on recovery, the patient began the next course. Over 60 courses of placebo, 38 attacks occurred (63%) (17/34 attacks severe), versus 7 attacks during 60 courses of colchicine (12%; p<0.001) (1/7 attacks severe). The study was discontinued when planned interim analysis showed a benefit of colchicine over placebo.

Goldstein and Schwabe (1974) reported 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. Over 3 months, 59 attacks occurred in 9/10 patients on placebo, versus 5 attacks in 2/10 patients on colchicine (p<0.002). Overall, 80% of patients had no attacks during colchicine treatment versus 10% of patients on placebo.

Zemer et al (1974) reported a double-blind crossover study in 22 patients who received in random order 2 month's treatment with 0.5 mg colchicine twice daily or placebo. In the first 2 month period, the colchicine group had significantly fewer attacks (mean 1.15 per patient, n=10) versus placebo (mean 5.25 per patient, n=10) (p<0.01). In 13 patients who completed the crossover study, there were significantly fewer attacks on colchicine than on placebo (p<0.01); the mean decrease in the number of attacks on colchicine was 3.85. During the 2 months on colchicine, 11 patients had fewer attacks than on placebo, 1 patient had more attacks and there was no change for 1 patient.

Kallinich et al. (2007) published treatment recommendations for use of colchicine in children and adolescents with FMF. 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 made and continue long term, with dose adjusted for age and renal function.

The recommended starting dose for children <5 years of age is 0.5 mg/day; for children 5-10 years is 1 mg/day; for children > 10 years of age is 1.5 mg/day. In patients who do not respond clinically to the standard dose or who are high risk for amyloidosis, the dose may be increased, incrementally, up to a maximum of 2.0 mg/day to control disease.

Hentgen et al (2013) reported clinical expert consensus on dose recommendations for adults with FMF as being 1 – 3 mg/day and for children before puberty, up to 2 mg/day.

IV.5 Clinical Safety

Colchicine has been used in clinical practice for decades and its safety profile is well known.
As this is a well established use application, the applicant has documented effects of colchicine through reference to published studies. The bibliographic search supporting the expert clinical review submitted was conducted within the NLM PubMed®

Medline and Embase® databases, as well as within the Cochrane Database of Systematic Reviews, standard medical texts, clinical practice guidelines and other general RCT internet searches.

Safety data from clinical studies
The most frequent side effects of colchicine are gastrointestinal (diarrhoea (23%), vomiting (17%), nausea (4% to 17%) and pharyngolaryngeal pain) (Sadiq 2019). These effects are dose related, may arise after a latent period of hours post dose, and may herald impending colchicine toxicity; the drug should be discontinued. High-dose colchicine (4.8 mg total over six hours) is associated with significantly more diarrhoea (70%), vomiting (17%) and other adverse events than a low-dose (1.8 mg total over one hour) regimen (Terkeltaub 2010, Wechalekar 2014).

Serious adverse events and death
Large doses of colchicine may cause GI haemorrhage, skin rash and renal and hepatic damage. Colchicine may also be associated with haematological, neuromuscular and dermatological toxicity. (Wilbur 2004, Dalbeth 2014, Underwood 2015, Kwon 2017, Slobodnick 2018, Robinson 2019).

Bone marrow depression with agranulocytosis, leucopenia, thrombocytopenia and aplastic anaemia may occur, especially during intoxication. On a review of i.v. colchicine treatment, haematologic toxicity appeared between the third and eighth days of drug administration, but most patients had gastrointestinal and neurologic toxicities before or at the onset of severe haematopoietic suppression; oral treatment appeared safer. (Levy 1991). As haematological changes may be gradual or sudden in onset, the blood count should be checked periodically, and colchicine treatment immediately discontinued if blood dyscrasia arises. Known blood dyscrasia is a contraindication of colchicine treatment.

Fatalities have been reported in the literature, with risk factors during colchicine therapy including intravenous dosing, renal insufficiency without dose adjustment, or with concomitant CYP3A4 inhibitor intake.

Special populations
Colchicine is indicated in children for the treatment of Familial Mediterranean Fever (FMF). Given the prophylactic doses used in children with FMF, close monitoring for signs and symptoms of toxicity is imperative to maintain a positive benefit-risk balance of prophylaxis in FMF children (Ozen 2016).

FMF is predominant in persons of non-Ashkenazi Jewish, Arabic, Turkish and Armenian descent. Safety data arises from paediatric use as treatment begins at a young age. Thus far, no specific safety issues or concerns have been identified, particular to use in the paediatric population.

In a study of the effects of a single oral dose of colchicine 1 mg in six healthy male adults and four elderly females, the mean absolute bioavailability was similar (44% and 45%) in the two groups. Mean peak plasma levels were lower (5.5 ng/ml) in younger males than in elderly females (12 ng/ml) and occurred earlier (62 minutes and 87 minutes after dosing respectively) (Rodchi 1994). In the elderly or debilitated patients, who may be susceptible to cumulative toxicity, particular attention should be paid to comorbidities such as cardiac, hepatic or gastro-intestinal disease and to the potential for drug interactions to occur with concomitant medications (Fravel 2011).

Ten to twenty percent of absorbed colchicine is excreted in the urine. In a single-dose, open-label study of the difference in PK level of colchicine in subjects with renal impairment including end-stage renal disease, a single oral 0.6 mg dose of colchicine was evaluated in 3 cohorts of 8 subjects with either: good health & normal renal function; mild, moderate, or severe renal impairment; or end-stage renal disease (ESRD), following haemodialysis. Patients with mild or moderate renal impairment or those actively receiving haemodialysis did not show accumulation of colchicine; those with severe renal failure showed a doubling of exposure. All patients with renal impairment taking colchicine should be closely monitored; many such patients will have comorbidities and be taking other medications (Wason 2014).
Yang et al. (2010) estimate that patients with end-stage renal disease who require dialysis show a 75% reduction in colchicine clearance.

In the European Alliance of Associations for Rheumatology (EULAR) guideline on gout management, colchicine dose reduction or dose interval lengthening is advocated for patients with moderate kidney disease (Richette 2017). Colchicine is contraindicated in patients with severe renal impairment.

Myotoxicity has been reported with colchicine use, typically in men aged 50 to 70 years with renal impairment (Stamp 2014), particularly in patients after renal or cardiac transplant. The EULAR guideline recommends that renally impaired patients taking

colchicine should undergo six monthly creatine kinase tests and state that both patients and physicians should be aware of the potential for neuro- and myotoxicity when renally impaired patients are treated with colchicine (Richette 2017).

As colchicine is largely metabolised by hepatocytes and is part eliminated by the liver, clearance of colchicine may be significantly reduced and the plasma half-life prolonged in patients with chronic hepatic impairment, compared to healthy subjects. Careful monitoring of patients with mild to moderate hepatic impairment for signs of toxicity is recommended and dose reduction may be considered in these patients (Leung 2015, Robinson 2019). In some subjects with mild to moderate cirrhosis, the clearance of colchicine is significantly reduced and plasma half-life prolonged compared to healthy subjects. No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C). Colchicine is contra-indicated for patients with severe hepatic impairment.

Drug interactions
Colchicine is a substrate for both CYP3A4 and the transport protein P-glycoprotien (P-gp). In the presence of CYP3A4 or P-gp inhibitors, the concentrations of colchicine in the blood increase and potentially serious toxicity may occur; fatal cases have been reported (Finkelstein 2010). In patients taking a moderate or potent CYP3A4 or P-gp inhibitor concomitantly with colchicine, with normal renal and hepatic function, the colchicine dose should be reduced and the patient closely monitored for signs of colchicine toxicity, or colchicine dose interrupted (Khanna 2012; Terkeltaub 2011; Davis 2013). Colchicine is contra-indicated in patients with renal or hepatic impairment who are taking a P-gp inhibitor or a strong CYP3A4 inhibitor.

P-gp, an efflux pump, regulates the absorption and tissue distribution of colchicine, as well as colchicine excretion via the biliary tract and kidneys.Interactions with P-glycoprotein inhibitors, such as ciclosporin, verapamil, quinidine, pravastatin, atorvastatin and other statins, azithromycin or digoxin, could increase intracellular levels of colchicine by altering bioavailability and reducing hepatic and/or renal elimination (Stockley 2015).Inhibition of P-gp-regulated colchicine transport by ciclosporin and verapamil has been demonstrated in non-clinical studies and has also been suggested for digoxin (deLannoy 1992).

Concomitant administration of inhibitors or substrates of CYP3A4 can inhibit colchicine metabolism and lead to concentration-related toxicity e.g. amiodarone, cimetidine, macrolide antibiotics, calcium channel antagonists, statins, HIV protease inhibitors and anti-fungal azole compounds (Stockley 2015).

An open, non-randomised study of the pharmacokinetic interactions of single oral doses of 0.6 mg colchicine with known inhibitors of CYP3A4 and/or P-gp has been reported (Terkeltaub 2011). Peak plasma concentrations and the exposure of colchicine increased by between 100% and >200% when administered in combination with ciclosporin, ketoconazole, ritonavir or clarithromycin comparison with colchicine alone (Terkeltaub 2011, Davis 2013).

Based on published in-vivo studies, a 4-fold reduction in colchicine dosage is recommended when co-administered with a P-gp inhibitor and/or a strong CYP3A4 inhibitor. A two-fold reduction in colchicine dosage is recommended when co-administered with a moderate CYP3A4 inhibitor.

In addition to PK drug-drug interactions, colchicine may undergo pharmacodynamic drug interactions (Finkelstein 2010). With concomitant dosing there may be additive neurotoxic, nephrotoxic or myotoxic effects. Combination with macrolide antibiotics may increase the risk of potentially serious pancytopenia, particularly in patients with renal impairment. Use of colchicine with ciclosporin, digoxin or lipid-regulating agents such as statins or fibrates may have an additive effect in inducing myopathy. Use with ciclosporin may increase nephrotoxicity. As colchicine shows moderate binding to plasma albumin, there is a theoretical risk of interactions with other protein-bound drugs. Reversible malabsorption of cyanocobalamin (vitamin B12) may be induced by an altered function in the intestinal mucosa.

Overdose
Colchicine has a narrow therapeutic index and is toxic in overdose, particularly in renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age. The literature contains reports of cases of both intentional and unintentional overdose, including deaths (Dalbeth 2014). All patients with suspected overdose should be referred for immediate medical evaluation, even if asymptomatic, as symptoms can be delayed.

Colchicine overdose is characterised by gastrointestinal symptoms (nausea, vomiting, abdominal pain, haemorrhagic gastroenteritis) and volume depletion, electrolyte abnormalities, leucocytosis and hypotension in severe cases. Multiple organ failure, which may be fatal, usually occur 24 to 72 hours after overdose, but may occur as late as seven days later. If the patient survives, recovery may be accompanied by rebound leukocytosis and reversible alopecia starting about one week after the initial ingestion.

No antidote is available and haemodialysis is ineffective. Gastric lavage within one hour of acute poisoning and oral activated charcoal in adults who have ingested more than 0.1 mg/kg bodyweight within 1 hour of presentation and in children who have ingested any amount within 1 hour of presentation should be considered. Subsequent treatment is symptomatic and supportive. In the literature, the lethal dose varies widely (7 – 65 mg single dose) for adults, with fatality is generally seen with administration of doses greater than 0.5 mg/kg (Finkelstein 2010).

Post-authorisation experience

The active substance colchicine is authorised for the claimed indication in many EU member states and in other jurisdictions. From regulatory agency databases in Europe and USA, the most frequent adverse reactions reported are gastrointestinal (diarrhoea, nausea, vomiting), renal (acute kidney injury) and drug interactions. The relatively high frequency of gastrointestinal adverse reactions and the risk of interactions with medicines that inhibit CYP3A4 and P-gp are in keeping with the known safety profile of colchicine.

Risk Management

A Risk Management Plan, version 1.1, dated 10th May 2021 has been submitted, 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 Halewood 500 microgram tablets. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

The safety and efficacy profile of colchicine in the indications applied for are well known.

As a well-established use application, the applicant has submitted appropriate literature to support this application. The applicant has bridged their product to those in the literature and provided supportive in vitro dissolution data.

The applicant has justified the bio-inequivalence seen in the study submitted in the past.

V. OVERALL CONCLUSIONS

From a quality perspective the overall assessment outcome for Colchicine Halewood 500 microgram Tablets is positive.

Using the published literature, the applicant has documented the safety and efficacy of colchicine in the form of Colchicine Halewood 500 microgram Tablets.

Bioequivalence is not required to be shown for this type of application.

The SmPC is consistent with that of the similar colchicine medicines, for the indications applied for, on the EU market.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Colchicine Halewood 500 microgram Tablets, from Halewood Chemicals (Ireland) Ltd, demonstrated adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile, and therefore granted a national marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	CRN0096FM	SmPC, IPAR and PIL	11th April 2025	10th April 2030