VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

- Gout[i]

Gout has a worldwide distribution. In the United Kingdom from 2000 to 2007, the estimated occurrence of gout is 5.9% in men and 2% in women, increasing with advancing age. The age limits of gout are 30-60 years.
About 90% of patients with gout are unable to remove sufficient urate (a mineral that is an end-product of certain foods) from the body with urine and thereby urates can build up in the body tissues or crystalize within the joints. Most of the remaining patients either over consume purines (an organic compound found in virtually all foods which is turned into uric acid when the body breaks down the purines) or produce excessive amounts of uric acid.
Treatment of gout is important to relieve pain; to prevent worsening of the disease; and to prevent storage of urate crystals in the kidneys, which may produce kidney stones or urate nephropathy (a rapidly decreasing kidney function).

VI.2.2 Summary of treatment benefits[ii]

Acute gout
The efficacy of colchicine in acute gout has been proven in two relevant studies performed on 146 patients. One study proved that both colchicine low-dose treatment (1.8mg) and high-dose treatment (4.8mg) are significantly more effective than placebo (a substance with no medicinal effect), with 37.8% responding to the treatment in the low-dose group, 32.7% responding to treatment in the high-dose group, and 15.5% responding to the treatment in the placebo group. Another study showed that a significantly greater proportion of the colchicine-treated patients responded within 48 h 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).

Prevention of Gout Flares
Clinical studies have reported significant reductions in flares when colchicine was given along with allopurinol or probenecid compared with urate lowering treatment alone. Patients in the colchicine/probenecid group had a significantly lower rate of gout flares per month than patients receiving placebo. Acute gout flares occurred in 33% of the allopurinol/colchicine patients (21 patients) and 77% of the placebo patients (22 patients).

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Decrease in production of cells responsible for providing immunity, carrying oxygen, and/or those responsible for normal blood clotting (severe bone marrow depression)	Colchicine causes severe decrease in production of cells responsible for providing immunity, carrying oxygen, and/or those responsible for normal blood clotting (agranulocytosis, aplastic anaemia, and thrombocytopenia). The change in blood counts may be gradual or very sudden. Aplastic anaemia in particular has a high mortality rate. Colchicine should be immediately discontinued and a full blood investigation should be conducted in case patients develop signs or symptoms that could indicate a decrease in blood cell production, such as fever, inflammation in the mouth, sore throat, prolonged bleeding, bruising or skin problems is included.	Yes, by performing periodic blood tests. Caution is advised in patients with abnormalities in blood counts.
Drug interaction with some hepatic enzymes inhibitors (Drug interaction with CYP 3A4 and P-glycoprotein inhibitors)	Colchicine is a substrate for both CYP3A4 and transport protein P-glycoprotein (hepatic enzymes). In the presence of CYP3A4 and P-glycoprotein inhibitors, the concentrations of colchicine in the blood increases. Toxicity, including fatal cases, have been reported during concurrent use of CYP3A4 and P-glycoprotein inhibitors such as macrolides (clarithromycin and erythromycin), cyclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel	Yes, by adjusting the dosage if treatment with a P-glycoprotein inhibitor or a potent CYP3A4 inhibitor is necessary in patients with normal renal and hepatic function. Concomitant use of these inhibitors with colchicine should be avoided in patients with renal or hepatic impairment.

Risk	What is known	Preventability
	blockers (verapamil and diltiazem), and colchicine. Grapefruit juice should not be drunk together with colchicine.	
Muscle disease including breakdown of muscle tissue (Myopathy and rhabdomyolysis)	The risk of breakdown of muscle tissue is increased by a combination of colchicine with statins, fibrates, ciclosporin or digoxin.	No specific method is known for prevention of this risk.
Use in patients with known hypersensitivity (allergy) to colchicine or to its excipients	Colchicine can cause hypersensitivity reactions in patients with known hypersensitivity to colchicine or to the excipients.	Colchicine should not be used in patients who are sensitive to colchicine or any of the excipients listed.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use of colchicine in patients where the usage is contraindicated (off-label use including haemodialysis and severe renal impairment, lactose intolerance)	The total removal of colchicine from the body is reduced in patients with end-stage renal disease undergoing dialysis. In addition, colchicine is not removed from serum by haemodialysis. Furthermore, the product contains lactulose and patients with lactose intolerance should not take this product. Therefore, if colchicine is used in these patients, they may be at increased risk of adverse events.
Overdose	There is only a slight difference between an effective dose of colchicine and an overdose, because colchicine has a narrow therapeutic index (range of drug dosages which can treat the disease effectively whilst still being safe). In addition, the administration of certain drugs together with colchicine or administration in certain patient groups may increase the risk for colchicine toxicity. However, the safety profile is well-known and there is substantial information regarding the proposed doses. Therefore, signs of overdose can be monitored.
Medication errors	Colchicine has a narrow therapeutic index, so there is only a slight difference between an effective dose and an overdose of colchicine. In addition, the administration of certain drugs together with colchicine or administration in certain patient groups may increase the risk for colchicine toxicity.

Missing information

Risk	What is known
Use in patients with reduced cardiac function (Use in patients with cardiac impairment)	Caution is advised in patients with reduced cardiac function.
Use in patients with reduced liver function (Use in patients with hepatic impairment)	Limited data exist in the literature on the behaviour of colchicine in the body of patients with reduced liver function.
Use in patients having problems with the digestive system (Use in patients with	The most frequently reported adverse events concern the digestive system such as diarrhoea, nausea, vomiting, abdominal pain and cramping. The events occur approximately

Risk	What is known
gastrointestinal disease)	8 to 12 h after oral administration in the majority of patients, especially when maximal doses are used. Therefore, caution is advised in patients having problems with the digestive system.
Use in patients with reduced kidney function (Use in patients with renal impairment)	The total removal of colchicine from the body was reduced 4-fold in patients with end-stage kidney disease undergoing dialysis. There is no direct evidence from clinical studies, nor from the marketing experience supporting that colchicine is contraindicated in patients with severe reduced kidney function. However, due to the narrow therapeutic index, it is recommended that colchicine is not used by these patients. The impact of mild to moderate renal impairment on the behaviour of colchicine in the body is not known, however, colchicine should be used with caution in these patients.
Use in elderly patients (> 65 years of age)	The adverse event profile of colchicine was comparable in young (18-30 years of age) and elderly (>60 years old) healthy subject who received a single 0.6 mg dose of colchicine, with the exception of increased blood pressure that was more often reported by elderly than by young subjects. The increased reporting rate may reflect an underlying condition of hypertension in the elderly. Furthermore, since the elderly are more likely to have significant reduced kidney or liver function, they may be more at risk.
Use during pregnancy and lactation	There are no adequate and well-controlled studies with colchicine in pregnant woman, but findings from the literature suggest that although colchicine crosses the placenta, when given in therapeutic doses it does not adversely affect reproductive potential in males or females, nor does it have other detectable untoward effects in mothers and children. Colchicine is excreted into breast milk at concentrations similar to those found in the mother but no untoward effects have been observed in breast-fed children. Limited information suggests that exclusively breast-fed infants receive less than 10 percent of the dose taken by the mother.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for colchicine.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
NA	NA	NA	NA

Version	Date	Safety Concerns	Comment
2.0	07-10-2014	Addition of the following risks to the RMP: Identified risks: - Use in patients with known hypersensitivity to colchicine or its excipients Potential risks: - Off-label use (including haemodialysis and severe renal impairment, lactose intolerance) - Overdose - Medication error Missing information: - Use in patients with cardiac impairment - Use in patients with hepatic impairment - Use in patients with gastrointestinal disease - Use in elderly patients (> 65 years of age) - Use during pregnancy and lactation Removal of the risk "colchicine-induced toxicity".	The RMP was updated based on Day 70 Preliminary Assessment Report from UK.
3.0	21-01-2015	The risks are not changed.	The RMP was updated based on Day 145 PAR, that requested PI changes with impact on the proposed RMMs.
3.1	04-03-2015	The risks are not changed.	The RMP was updated based on Day 180 and Day 195 PAR, that requested PI changes with impact on the proposed RMMs.