Risk Management Plan

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Ulcerative colitis is an autoimmune disease (disease in which the body's own immune system attacks elements of the digestive system). Common features of ulcerative colitis are diarrhea, bloody stools, weight loss, abdominal pain, fever, and fatigue. The exact cause of ulcerative colitis remains unclear. Ulcerative colitis is restricted to the large intestine and the rectum and involves only the innermost part of the intestinal wall, with continuous areas of sores and no normal tissue. Occurrence ranges from 37 to 246 cases per 100,000 persons for ulcerative colitis.

VI.2.2 Summary of treatment benefits

The most common treatments for ulcerative colitis include a group of medicines called aminosalicylates that include medication as sulfasalazine and mesalazine. Mesalazine is the primary treatment for mild to moderate ulcerative colitis. In addition, many of the side effects associated with sulfasalazine therapy have been attributed to the sulfapyridine moiety (a specific part of this medicine) and most patients unable to tolerate sulfasalazine because of allergic reactions or side effects can be transferred to mesazaline without these side effects occurring [Dew et al. (1983), Campieri et al. (1984), Donald et al. (1985), Rao et al. (1987) in **Martindale** 37th edition (2011)]. Mesalazine is not generally associated with sulfasalazine's side effects on sperm. In addition, 80% of patients intolerant to sulfasalazine will tolerate mesazaline without problems [D'Haens et al. (2004) in **Martindale** 37th edition (2011)]. In mild to moderate active disease mesalazine has response rates between 40%–70% and remission rates of 15%–20%; mesalazine has been shown to be safe in short-term use with a dose-response efficacy without dose-related toxicity [**Karagozian** et al. (2007)]. In patients with extensive mild to moderate active ulcerative colitis defined by involvement beyond the splenic flexure (a part of the colon), adding a mesalazine enema to an oral regimen would provide additional benefit for patients with extensive mild to moderate active ulcerative colitis [Marteau et al. (2005) in **Karagozian** et al. (2007)].

VI.2.3 Unknowns relating to treatment benefits

This product has been in use for many years and the safety profile of the active ingredient is well established, therefore almost all different populations are exposed and the effects of mesalazine on these different populations are known. However exposure to mesalazine should be avoided when pregnant or lactating. In addition, there is no dosage recommendation for children.

VI.2.4 Summary of safety concerns

Mesalazine belongs to a group of medicines called aminosalicates, which are medicines against ulcerative colitis. In the treatment of ulcerative colitis mesalazine is used to keep the disease in control and also during severe phases of the disease. Mesalazine is a medicine, which is available in pharmacies and has been on the market for a considerable period of time. It is a safe product when used for the above indication. Nonetheless, the use of this product can carry some risks, which people should be aware of before taking the product (see the table below).

Summary of safety concerns – important identified risks

Risk	**What is known**	**Preventability**
Hypersensitivity reactions	Hypersensitivity reactions (allergic reactions) can occur with and without previous exposure to mesalazine. The frequency of the reactions is very rare (<0.01%). The reactions can be mild but also very serious. Treatment for all these reactions is available and will result in a quick recovery of the patient.	When it is proven that the allergic/hypersensitivity reaction is due to mesalazine or one of the excipients, it can be easily prevented by not taken the drug again. A previous allergic reaction to mesalazine is also a contraindication for the use of mesalazine so this patient population will then be excluded from the use of mesalazine.
Kidney function disorders	It is recommended that mesalazine is used with extreme caution in patients with mild to moderate renal impairment. The concurrent use of mesalazine with other known nephrotoxic agents (medication that is toxic to the kidneys) may increase the risk of renal reactions. Known side effects of the use of mesalazine are abnormal renal function including interstitial nephritis (inflammation of the kidney), nephrotic syndrome (a condition where protein in the blood is highly excreted into urine) and urine discolouration (very rare: ≥0.01% and <0.1%). These are usually very serious events.	A contraindication for the use of mesalazine is patients with severe kidney function disorders. By excluding these patients from the use of mesalazine, the risk of kidney function disorders can be prevented. Furthermore this risk can prevented by monitoring the renal function regularly especially during the beginning of the treatment. Or when used in combination with other known toxic agents.
Liver function disorders	Mesalazine is not indicated for patients with severe impaired liver function. Caution is recommended in patients with impaired liver function. Known side effects of the use of mesalazine are abnormalities in hepatic function and hepatotoxicity (toxicity to the liver), including hepatitis (inflammation of the liver), cirrhosis (degeneration of the liver cells) and hepatic failure (inability of the liver to perform its function)). These are usually very serious events and very rare (≥0.01% and <0.1%).	A contraindication for the use of mesalazine is patients with impaired liver function. By excluding these patients from the use of mesalazine, the risk of liver function disorders can be prevented. Furthermore this risk can be prevented by monitoring the liver function regularly.
Blood dyscrasias	Serious blood dyscrasias (diseases of the blood) have been reported rarely with mesalazine. Blood tests should be performed if the patient develops unexplained bleeding, bruising, purpura (discoloration of the skin caused by extravasation of blood into the skin), anaemia (decrease of red	When there is suspicion or evidence of blood abnormalities due to mesalazine this can be investigated by performing blood tests. Treatment should be stopped if there is suspicion or evidence of blood abnormalities and resulting in less serious effects.

Risk	What is known	Preventability
	blood cells), fever or sore throat. Concomitant treatment with mesalazine can increase the risk of blood dyscrasia in patients receiving the medications azathioprine or 6-mercaptopurine. Known side effects of the use of mesalazine are diseases concerning an abnormal low amount of white blood cells in the blood (called leucopenia, granulocytopenia, neutropenia granulocytopenia, agranulocytosis), aplastic anaemia (deficiency of all type of blood cells) and thrombocytopenia (deficiency of the platelets in the blood). These events are rare (≥0.01% and <0.1%). The events anaemia (decrease of red blood cells), eosinophilia (low amount of certain white blood cells, as part of an allergic reaction) and pancytopenia (deficiency of white, red blood cells and platelets) are very rare (<0.01%).	

Risk	What is known
Cardiovascular toxicity	It is stated that mesalazine can induce cardiovascular toxicity (heart and blood vessel toxicity), including pericarditis, myocarditis (both are inflammations of the heart), vasculitis (inflammation of the blood vessels), and left ventricular dysfunction (dysfunction of a certain part of the heart). Treatment should be discontinued on suspicion or evidence of these reactions.

Summary of safety concerns –missing information

Risk	What is known
Exposure during pregnancy	Mesalazine should not be used during pregnancy and breast feeding except when the potential benefits of the treatment outweigh the possible hazards in the opinion of the physician. Mesalazine is known to cross the placental barrier. Data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiologic data are available. There is no clear evidence of harm of mesalazine treatment during pregnancy.
Exposure during breast feeding	Mesalazine granules for rectal suspension should not be used during pregnancy and breast feeding except when the potential benefits of the treatment outweigh the possible hazards in the opinion of the physician. Mesalazine is excreted in breast milk. The mesalazine concentration in breast milk is lower than in maternal blood, whereas the metabolite - acetyl-mesalazine - appears in similar or increased concentrations.
Effect on fertility	Animal data on mesalazine show no effect on male and female fertility. There is no reference to the effect of meselazine on fertility in humans.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Details of the routine risk minimisation measures are provided in the product information.

Routine pharmacovigilance practice and appropriate product labeling are considered to be sufficient. Therefore, no additional risk minimisation measures are planned for any of the important identified risks, important potential risks, or missing information. No post-authorisation development plan is required.

VI.2.6 Planned post-authorisation development plan

No post-authorisation studies are planned and therefore this section is not applicable.

VI.2.7 Summary of changes to the risk management plan

Not applicable, since this is the first RMP of mesalazine.