Part VI: Summary of the risk management plan for PENTASA/QUINTASA (mesalazine)

This is a summary of the risk management plan (RMP) for PENTASA/QUINTASA. The RMP details important risks of PENTASA/QUINTASA, how these risks can be minimised, and how more information will be obtained about PENTASA/QUINTASA risks and uncertainties (missing information).

PENTASA/QUINTASA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PENTASA/QUINTASA should be used.

Important new concerns or changes to the current ones will be included in updates of PENTASA/QUINTASA's RMP.

I. The medicine and what it is used for

PENTASA/QUINTASA is authorised for treatment of mild to moderate ulcerative colitis and Crohn’s disease. See SmPC for the full indication. It contains mesalazine as the active substance and it is given by oral route of administration for tablets and granules and rectal route of administration for suppository and rectal suspension (enema).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PENTASA/QUINTASA, together with measures to minimise such risks and the proposed studies for learning more about PENTASA/QUINTASA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of PENTASA/QUINTASA is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of PENTASA/QUINTASA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PENTASA/QUINTASA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information

Important identified risks	Impairment of renal function including interstitial nephritis, renal insufficiency
	Impairment of hepatic function including hepatitis, cholestatic hepatitis
	Respiratory disorders including pneumonitis
	Blood dyscrasias including agranulocytosis, thrombocytopenia, aplastic anemia
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Impairment of renal function including interstitial nephritis, renal insufficiency	
Evidence for linking the risk to the medicine	The frequency with 95% CI is not known. The incidence of mesalazine associated interstitial nephritis appears to be low with tubulointerstitial nephritis as predominant. Fockens et al. reported that two (1.3%) of 154 patients receiving mesalazine for 1 year developed reversible renal insufficiency.[45] Hanauer et al. found that of 2,940 IBD patients treated with mesalazine for an average of 53 weeks, only eight (0.3%) had clinically significant elevations of blood urea nitrogen and/or serum creatinine during the study.[46] The United Kingdom Committee on Safety of Medicines also analysed serious ADRs for mesalazine from 1991 to 1998. From a total of 2.8 million prescriptions issued during this time, they found 29 cases of interstitial nephritis, giving a complication rate of 10.4 per million prescriptions written.[47]
Risk factors and risk groups	The drug is not recommended for use in patients with renal impairment (see CCDS/Product Information).
Risk minimisation measures	Addressed in the Product Information by way of advising on taking the specific clinical action beyond standard care to determine renal and urinary status prior to and during treatment with mesalazine. Mesalazine is further not recommended for use in patients with renal impairment and the product information advises that nephrotoxicity should be suspected in patients developing renal dysfunction during treatment and that the concurrent use of other known nephrotoxic agents should increase the monitoring frequency of renal function.

Important identified risk: Impairment of hepatic function including hepatitis, cholestatic hepatitis	
Evidence for linking the risk to the medicine	The frequency with 95% CI is not known. Few cases have been reported with acute drug induced liver injury (DILI) during mesalazine therapy. According to a UK study, the incidence of mesalazine generating acute DILI is 3.2 cases per million prescriptions[12] and a Swedish study showed elevated serum alkaline phosphatase in 5% of ulcerative colitis (UC) patients.[50]
Risk factors and risk groups	Not specified
Risk minimisation measures	Addressed in the Product Information by way of advising on

	taking the specific clinical action beyond standard care to assess liver function parameters like AST or AST prior to and during treatment. The product information further advises that caution is recommended in patients with impaired liver function.

Important identified risk: Respiratory disorders including pneumonitis	
Evidence for linking the risk to the medicine	The frequency with 95 % CI not known. Respiratory disorders, potentially mesalazine related, have been reported, albeit uncommonly. The pulmonary tract can have manifestations including among others: interstitial infiltrates, consolidation, pleural effusions, alveolitis, and bronchiolitis. Cases of pulmonary eosinophilia and bronchiolitis obliterans organizing pneumonia (BOOP) have also been reported extremely rarely, including interstitial infiltrates, consolidation and pleural effusions. A review of mesalazine-related pulmonary disorders in patients with IBD included few patients with evidence of peripheral eosinophilia and with eosinophilia in the broncho-alveolar lavage fluid.[51,52,53,54] Respiratory disorders are also associated with IBD such as extra-intestinal manifestations.
Risk factors and risk groups	Paediatric and elderly patients, advanced human immunodeficiency virus (HIV) and patients with IBD. Patients with pulmonary disease, in particular asthma, should be carefully monitored.
Risk minimisation measures	Addressed in the Product Information by way of advising on taking the specific clinical action to very carefully monitor patients with pulmonary disease, in particular asthma, during a course of treatment. The method of monitoring is left to the discretion of the treating physician due to the variety of conditions being included in the risk.

Important identified risk: Blood dyscrasias including agranulocytosis, thrombocytopenia, aplastic anaemia	
Evidence for linking the risk to the medicine	The frequency with 95 % CI is not known. According to the literature, mesalazine-induced blood dyscrasias are considered very rare and therefore of a low incidence. Jick et al. studied the prevalence of haematological ADRs among patients receiving 5-ASA preparations in United Kingdom (General Practice Research Database) and no cases of haematological ADRs were found among the 4,004 IBD patients receiving mesalazine.[55]
Risk factors and risk groups	Patients with concomitant treatment with azathioprine (AZA), or 6-mercaptopurine (6-MP) or thioguanine.
Risk minimisation measures	Addressed in the Product Information by way of advising on taking the specific clinical action to perform blood tests for differential blood counts prior to and during treatment.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of PENTASA/QUINTASA.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for PENTASA/QUINTASA.