Part VI: Summary of the risk management plan

Summary of risk management plan for Litalgin (Metamizole sodium and pitofenone hydrochloride

This is a summary of the risk management plan (RMP) for Litalgin. The RMP details important risks of Litalgin, how these risks can be minimised, and how more information will be obtained about Litalgin's risks.

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

I. The medicine and what it is used for

Litalgin is authorised for colic pain in the gastrointestinal, biliary ducts and urinary tracts and bladder spasms. (See SmPCs for the full indication). It contains metamizole sodium and pitofenone hydrochloride as the active substance and it is given by oral/intramuscular/intravenous routes.

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

Important risks of Litalgin, together with measures to minimise such risks and the proposed studies for learning more about Litalgin'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.

Additional Measures to minimize the risks identified for medicinal products are:

- Direct Healthcare Professional Communication for the risk of “Agranulocytosis” and “Acute liver failure and drug-induced liver injury (DILI)”.
- Patient alert card for the risk of “Agranulocytosis”.

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

II.A List of important risks and missing information

Important risks of Litalgin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken. 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 Litalgin. 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).

Summary of safety concerns	
Important identified risks	Agranulocytosis and bone marrow depression
	Anaphylactic reaction/shock
	Acute liver failure and drug-induced liver injury (DILI)
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Agranulocytosis and bone marrow depression	
Evidence for linking the risk to the medicine	Reference Safety Information, Literature.
Risk factors and risk groups	Agranulocytosis has been reported in patients undergoing chemotherapy treatment for cancer, taking certain medications, including some anti-thyroid medications, antidepressants, antihistamines, and anticonvulsants, infection, Vitamin B12 or folate deficiency, leukemia or myelodysplastic syndromes, aplastic anemia or other diseases of the bone marrow, and family history of certain genetic diseases [81]. Specific risk factors for agranulocytosis were evaluated in a prospective survey performed by the International Aplastic Anemia and Agranulocytosis Study (IAAAS) in Europe and Israel from 1980 to 1986. According to the study the incidence rose sharply with age, only 10 percent of cases occurred in children and young adults, while more than 50 percent of cases occurred in patients over age 50 [88]. Agranulocytosis was almost twice as frequent in women, accounting for approximately 70 percent of cases. The gender difference may be due in part to greater consumption of medications at higher risk of causing agranulocytosis [7,88-90]. Other risk factors for agranulocytosis include: • A possible increase in risk in patients with infectious mononucleosis. • Underlying autoimmune disease. There is evidence for genetic susceptibility in certain populations.

Important identified risk: Agranulocytosis and bone marrow depression	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs sections: • 4.2 Posology and method of administration, • 4.3 Contraindications, • 4.4 Special warnings and precautions for use and • 4.8 Undesirable effects. • Other: o Removal of 100-tablet pack size from the market. o Recommendation to monitor the blood count of the patient, including differential count of leucocytes, on a weekly basis, if Litalgin is used for a longer period, over a week and if Litalgin is used during antibiotic treatment is included in the SmPC section 4.2. o A boxed warning text on one of the carton panels is as follows; This warns the user about SAEs, instructs the user to read the patient alert card before use, instructs to use the product for the shortest duration possible, and states that if the product is used for more than a week the blood count should be monitored weekly. **Additional risk minimisation measures:** • Direct Healthcare Professional Communication. • Patient alert card
Additional pharmacovigilance activities	• None

Important Identified Risk: Anaphylactic reaction/shock	
Evidence for linking the risk to the medicine	Reference Safety Information, Literature.
Risk factors and risk groups	Risk factors include a personal history of anaphylaxis, asthma or allergy, and familial history.

Important Identified Risk: Anaphylactic reaction/shock	
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs sections: • 4.3 Contraindications, • 4.4 Special warnings and precautions for use and • 4.8 Undesirable effects. **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	• None

Important Identified Risk (Acute liver failure and drug-induced liver injury (DILI))	
Evidence for linking the risk to the medicine	RSI and Medical Literature
Risk factors and risk groups	Several predisposing factors have been identified that may cause increased risk in developing DILI [103]. Patient risk factors such as genetic predisposition, gender (females), pregnancy, comorbidities including preexisting liver disease, and indications for therapy (e.g., Hepatitis C). Smoking and alcohol consumption is also known to increase toxicity. Furthermore, drug-related factors, such as daily dose (>50mg/day), metabolic profile, and class effect can also contribute to DILI. Furthermore, drugs that induce expression of P450 (CYP) appear to be associated with greater risk of DILI.
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs sections: • 4.4 Special warnings and precautions for use and • 4.8 Undesirable effects. **Additional risk minimisation measures:** • Direct Healthcare Professional Communication.

Important Identified Risk (Acute liver failure and drug-induced liver injury (DILI))	
Additional pharmacovigilance activities	• None

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 Litalgin.

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

There are no studies required for Litalgin.