

RISK MANAGEMENT PLAN – PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA (Metamizole)

This is a summary of the risk management plan (RMP) for NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA. The RMP details important risks of NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA and how these risks can be minimized.

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

Important new concerns or changes to the current ones will be included in updates of NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA is authorized for Severe or resistant pain and fever (approved therapeutic indications of the medicinal product may vary depending on nationally authorized marketing authorizations) (see local SmPC for the full indication).

NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA contains metamizole as the active substance and it is given through oral, rectal and parenteral routes of administration.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA, together with measures to minimize such risks and the proposed studies for learning more about NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA's risks, are outlined in the next sections.

Measures to minimize 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 authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment 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 NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered or 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 NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA. 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 (eg, on the long-term use of the medicine);

Table 17 - List of important risks and missing information

Important identified risks	Agranulocytosis Pancytopenia Drug induced liver injury: non-direct mechanism
Important potential risk	None
Missing information	None

II.B. Summary of important risks

Table 18 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Agranulocytosis

Agranulocytosis	
Evidence for linking the risk to the medicine	ICSRs and literature
Risk factors and risk groups	Although this has not been fully established, patients with a previous history of hypersensitivity to pyrazolone derivatives (drugs similar to

Agranulocytosis	
	metamizole) as well as patients with bone marrow impairment could constitute a high-risk group and, thus, should not receive metamizole.
Risk minimization measures	Routine risk minimization measures: CCDS sections 4, 5 and 9 PIL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS in Egypt (IMAGE)

CCDS: Company Core Data Sheet; ICSR: Individual Case Safety Report; PIL: Patient Information Leaflet; PASS: Post-Authorization Safety Study.

Table 19 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Pancytopenia

Pancytopenia	
Evidence for linking the risk to the medicine	ICSRs
Risk factors and risk groups	Although this has not been fully established, patients with a previous history of hypersensitivity to pyrazolone derivatives (drugs similar to metamizole) as well as patients with bone marrow impairment could constitute a high-risk group and, thus, should not receive metamizole. Elderly patients and concomitant treatment with methotrexate were identified as risk factors for fatal outcome.
Risk minimization measures	Routine risk minimization measures: CCDS sections 5 and 9 PIL section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS in Egypt (IMAGE)

CCDS: Company Core Data Sheet; ICSR: Individual Case Safety Report; PIL: patient Information Leaflet; PASS: Post-Authorization Safety Study.

Table 20 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Drug induced liver injury: non-direct mechanism

Drug induced liver injury: non-direct mechanism	
Evidence for linking the risk to the medicine	PSUSA/00001997/202003, ICSRs and literature
Risk factors and risk groups	A relationship between the incidence of DILI and older age was observed in a prospective DILI study from Iceland. However, this does not necessarily indicate causal relationship; rather it might reflect an increased number of drugs prescribed with older age.

Drug induced liver injury: non-direct mechanism	
	Females and males appear to have a similar risk of DILI although patients with chronic liver disease may not in general have an increased risk of developing DILI, the consequences of a DILI episode in these patients might be more severe. Diabetes mellitus has also been associated with increased risk of mortality in patients with DILI, and dyslipidemia was associated with increased risk of chronic DILI in patients followed up within the Spanish Hepatotoxicity Registry. (23)
Risk minimization measures	Routine risk minimization measures: CCDS sections 5 and 9 PIL sections 2 and 4 Additional risk minimization measures: DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

CCDS: Company Core Data Sheet; DHPC: Direct healthcare Professional Communication; DILI: Drug Induced Liver Injury; ICSR: Individual Case Safety Report; PIL: Patient Information Leaflet; PSUSA: Periodic Safety Update Report Single Assessment.

II.C. Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of NOVALGINE, NOVALGIN, ALGOPYRIN and NOVALGINA.

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

Table 21 - Other studies in post-authorization development plan

Post-authorization safety study IMAGE: Incidence of metamizole induced agranulocytosis in Egypt: a case population study

Purpose of the study:

Primary:

- To evaluate the incidence of agranulocytosis in the general population in Egypt and among metamizole users in Egypt.

Secondary:

- To evaluate the incidence of aplastic anemia and pancytopenia in the general population in Egypt and among metamizole users in Egypt.