
VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

A bladder spasm occurs when the bladder muscle squeezes suddenly without warning, causing an urgent need to release urine. The spasm can force urine from the bladder, causing leakage. This condition is called urge incontinence or over-active bladder (OAB). It is often associated with cramping pain and is sometimes perceived as a burning sensation. Abdominal cramping and pain is more common in women (12-55%) than in men (7-38%). Bladder spasms are most often associated with a urinary tract infection, recent lower abdominal or pelvic surgery, nerve or bladder muscle damage caused by disease or injury, in the elderly and in women during pregnancy, following childbirth, or after menopause.

Acute abdominal pain (stomach pain) is the most common complaint in 1.5% of physician office visits and 5% of emergency room visits. Usually the pain does not last long and is often due to a gut infection (infection in the gastrointestinal tract). There are many causes of abdominal pain. One of the common causes is Gallstones otherwise known as biliary colic, which is due to the gallstones obstructing the cystic duct or common bile duct. Colic pain in the gastrointestinal tract can have a variety of causes and can be associated with various anatomical structures. The median occurrence of gallstone disease in the largest population surveys in Europe ranges from 5.9 to 21.9% with the highest rates seen in Norway (21.9%) and former East Germany (19.7%), and the lowest rates in Italy (Chianciano 5.9% and Sirmione 6.9%). Renal colic is another type of abdominal pain and is a common emergency department presentation. It is caused by kidney stones. Kidney stones are crystals that form from chemicals in the urine. Usually, a stone develops because there is too much of one chemical present in the urine. The 2000 National Hospital Ambulatory Medical Care Survey of the United States estimated 1.1 million emergency department visits annually due to renal colic.

VI.2.2 Summary of treatment benefits

Metamizole is an ampyrone sulfonate analgesic (pain reliever), antispasmodic (spasm reliever) and antipyretic (fever reducer). Pitofenone is a spasmolytic agent (spasm reliever). The combination of metamizole and pitofenone have been studied in association with other drugs for the treatment of bladder spasms and colic pain in various studies. These studies showed that the spasmolytic with analgesic effect of metamizole was higher than other comparator products, and was very useful during colic attacks. In one study, 104 patients suffering from “severe” or “excruciating” colic pain received metamizole, tramadol and butylscopolamine and it was found that metamizole was significantly more effective in reducing the pain than tramadol and butylscopolamine. The effectiveness of metamizole when studied cumulatively in 11

studies, where 550 patients received metamizole, showed single dose metamizole had similar efficacy to other analgesics used in renal colic pain. Metamizole was also studied in intestinal and renal colic pain comparing with hyoscine-N-methyl-bromide and was found to be a better pain reliever. Given the well-established benefits of the components in the approved indications there are less known uncertainties.

VI.2.3 Unknowns relating to treatment benefits

No well-controlled studies involving pregnant or lactating women were conducted. However, it was found that metamizole and pitofenone is excreted in breast milk and hence should not be administered to pregnant or lactating women. The safety of metamizole and pitofenone in children is unknown and hence should not be administered to children.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Low blood count (Agranulocytosis and bone marrow depression)	Agranulocytosis and bone marrow depression is a rare adverse effect caused by metamizole and pitofenone.	The patient should be advised to immediately discontinue the treatment if any symptoms of agranulocytosis occur, and consult a doctor as soon as possible. White blood cell count should be monitored weekly during the long-term use (over one week). Metamizole and pitofenone should not be used in patients with impaired bone marrow function or agranulocytosis associated with previous drug treatment. A Patient alert card is provided to help patients to self-identify the symptoms and address the risk of low blood count and anaphylactic reaction / shock. A Letter is sent to Healthcare Professionals to inform them about the risks and preventability measures
Anaphylactic reaction / shock	Anaphylactic reaction and shock are rare and serious adverse	Metamizole and pitofenone should not be used in case of

Risk	What is known	Preventability
	effects caused by metamizole and pitofenone, requiring emergency treatment.	hypersensitivity to metamizole or other pyrazolone derivatives, pitofenone or other ingredients of the preparation. Metamizole and pitofenone should not be used in case of previously occurred asthma or anaphylactic reaction associated with the use of analgesics, or anaphylactic reaction associated with previous treatment with Litalgin If symptoms occur, the patient should immediately stop taking metamizole, and should consult a doctor as soon as possible. A Patient alert card is provided to help patients to self-identify the symptoms and address the risk of low blood count and anaphylactic reaction / shock.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	Not applicable

Missing information

Risk	What is known
None	Not applicable

VI.2.5 Summary of risk minimisation measures by safety concern

Metamizole and pitofenone 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 (PIL). The measures in these documents are known as routine risk minimisation measures.

Metamizole and pitofenone has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex 2 of the product

information which is published in Litalgin's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national competent authorities.

These additional risk minimisation measures are for the following risks:

Low blood count (Agranulocytosis and bone marrow depression)

Risk minimisation measure(s)
Remove the 100 tablet package size from the market: To minimize the unnecessary long-term use of the drug. Furthermore, in case of renewal of the prescription of the smaller package (30 tablet), the physician should take the opportunity to (i) remind the patient of the risk of agranulocytosis / ask any symptoms (ii) reconsider the need of modifying the treatment of the underlying disease or (iii) stop the treatment. Patient Alert Card: • To help the patients to self-identify the first symptoms of agranulocytosis and bone marrow depression, in order to prevent late diagnosis of agranulocytosis. • Instruct the patient, that when the symptoms occur the patients should be advised to immediately stop metamizole intake, and to consult a doctor as soon as possible. • Inform the patient that there is a need to weekly monitor the white blood cell count during a long-term (>one week) treatment of Litalgin. Direct Healthcare Professional (DHCP) Letter: • To use Litalgin only on-label and only for the shortest period of time needed. • Importance of awareness of the risk of agranulocytosis and to have an initial TBC (+WBC differential). • The current warnings in the SmPC and any potential changes to it. • The new risk minimization measures related to Litalgin use.

Anaphylactic reaction / shock

Risk minimisation measure(s)
Patient Alert Card: • To help the patients to self-identify the first symptoms of anaphylactic reaction / shock, in order to prevent late diagnosis. • Instruct the patient, that when the symptoms occur the patients should be advised to immediately stop metamizole intake, and to consult a doctor as soon as possible.

VI.2.6 Planned post authorisation development plan

Metamizole and pitofenone have been on the market for many decades; therefore, their efficacy and safety profile is well established. There is no planned post authorization development program.

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
2.0	31 October 2016	Important identified risk: Anaphylactic reaction / Shock	Anaphylactic reaction / Shock added as an important identified risk
3.0	24 February 2017	Agranulocytosis and bone marrow depression; Anaphylactic reaction / Shock	Patient alert card as an additional risk minimisation measure
3.0	24 February 2017	Agranulocytosis and bone marrow depression	Removal of questionnaire for systematic case follow-up from additional risk minimisation measures (RMP section VI.1.4) and included in routine risk minimization measures
3.0	24 February 2017	Agranulocytosis and bone marrow depression; Anaphylactic reaction / Shock	Modification of RMP public summary to be written for the lay reader in suitable language for the general public.