PART V. : SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ESPIDIFEN, ESPIDIDOL, SPEDIFEN, ZAFEN, SPIDIFEN, SPIDIDOL, SPIDIDOL ANALGESICO, FASPIC AND SPIFEN (IBUPROFEN ARGININE)

This is a summary of the risk management plan (RMP) for Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen. The RMP details important risks of Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen, how these risks can be minimised, and how more information will be obtained about ibuprofen arginine's risks and uncertainties (missing information).

The summary of product characteristics (SmPC) of Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen and their package leaflets give essential information to healthcare professionals and patients on how ibuprofen arginine should be used.

I. THE MEDICINE AND WHAT IT IS USED FOR

Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen are authorised for the symptomatic treatment of pain of mild to moderate intensity, such migraine, arthritis, ankylosing spondylitis and menstrual pain, dental pain, post-operation pain and osteoarthritis (see SmPC for the full indication). They contain ibuprofen arginine as active substances and they are given by oral route of administration (granules for oral solution 200 mg; effervescent tablets 200 mg; Tablets200 mg; oral drops 200 mg/ml; film-coated tablets 400 mg; granules for oral solution 400 mg; granules for oral solution 600 mg).

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen, together with measures to minimise such risks and the proposed studies for learning more about risks of these products, 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 Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely 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 Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen. 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	• Gastrointestinal bleeding, ulceration and perforation • Increased risk of bleeding • Use in patients concomitantly under treatment with other NSAIDs and cyclooxygenase-2- selective inhibitors. • Hypersensitivity /Allergic reactions and serious skin reactions • Cardiovascular and cerebrovasculat disorders • Renal impairment • Hepatic impairment • Use in pregnancy in last trimester/mother delivery complications • Use in elderly • The risk of renal insufficiency in dehydrated children • Hematological disorders • High dose and long term treatment
Important potential risks	• Use in patients concomitantly on acetylsalicylic acid • Influence of the NSAIDs on the deterioration of the course of infections • Use in early pregnancy • Off-label use
Missing information	None

II.B. Summary of important risks

Important identified risk: Gastrointestinal bleeding, ulceration and perforation	
Evidence for linking the risk to the medicine	Beside the most common abdominal pain, nausea, vomiting and diarrhoea, some severe gastrointestinal events including bleeding, ulcer and perforations may rarely occur with ibuprofen. These are

	serious conditions, with a chronic evolution that requires medical care and may lead sequelae. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	The gastrointestinal risk increases with dosage and duration of treatment and it is higher in case of preexisting ulcer and in the elderly. In this regards, caution is recommended when treating patients concomitantly taking other drugs that could increase risk of bleeding and ulceration (oral corticosteroids, anticoagulants, antiplatelet agents including acetylsalicylic acid, selective serotonin reuptake inhibitors).
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.3, 4.4, 4.5 and 4.8) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Increased risk of bleeding	
Evidence for linking the risk to the medicine	Ibuprofen may prolong bleeding time until 1 day after discontinuation of therapy through inhibition of platelet function. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Patients concomitantly on other drugs known to increase the risk of bleeding have additional risk as well as patients with history of gastrointestinal bleeding due to NSAIDs or other active bleeding.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.4 and 4.5) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Use in patients concomitantly under treatment with other NSAIDs and cyclooxygenase-2- selective inhibitors.	
Evidence for linking the risk to the medicine	NSAIDs and other COX-2 inhibitors induced gastrointestinal toxicity by systemic interactions with prostaglandin synthesis. The concomitant administrations of two or more of these drugs increase the risk of adverse reactions in the gastrointestinal tract. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Patients concomitantly on other NSAIDs or systemic corticosteroids.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.4 and 4.5) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Hypersensitivity /Allergic reactions and serious skin reactions	
Evidence for linking the risk to the medicine	Hypersensitivity and allergic reactions, ranging from cutaneous eruptions up to anaphylaxis, may also occur following a single dose of ibuprofen and may be life-threatening. Due to the severity of these reactions, the risk has been considered as an important one. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk factors are: known hypersensitivity to ibuprofen and past history of asthma, acute rhinitis, angioneurotic edema or other allergic-type reactions to NSAIDs.

Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.3, 4.4,and 4.8) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Cardiovascular and cerebrovascular disorders	
Evidence for linking the risk to the medicine	There are data suggesting that the use of ibuprofen in high doses (2,400mg daily) may be associated with a small increased risk arterial thrombotic events. Epiemiological studies do not suggest that low dose ibuprofen is associated with an increased risk of arterial thrombotic events. This is serious, life threatening event that require hospitalisation. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk factors are: hypertension, hyperlipidaemia, diabetes mellitus, and smoking congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.3, 4.4, and 4.8) and PIL
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Renal impairment	
Evidence for linking the risk to the medicine	Ibuprofen is known to cause disorders linked to impaired renal function ranging from edema to acute renal failure. These are serious, sometimes fatal reactions and may require hospitalization. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk factors are: medical history of renal function disorders, concomitant intake of diuretics. dehydratation in children and age.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.2, 4.3, 4.5, 4.8 and 4.9) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Hepatic impairment	
Evidence for linking the risk to the medicine	In rare cases, hepatic function abnormalities have been reported with ibuprofen. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Patients suffering from hepatic disorders may have additional risk.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.2, 4.3, 4.4 and 4.8) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Use in pregnancy in last trimester/mother delivery complications	
Evidence for linking the risk to the medicine	The use of ibuprofen during the third trimester may expose the fetus and the mother to serious risks i.e. cardiopulmonary toxicity and renal dysfunction (up to renal insufficiency) for the fetus and increased bleeding time and prolonged labour for the mother. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).

Risk factors and risk groups	Risk group: pregnant patients at the third trimester.
Risk minimisation measures	Risk minimization measures are addressed in the relevant section of the SmPC (4.6) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Use in elderly	
Evidence for linking the risk to the medicine	The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk group: elderly.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.2, 4.4) and PIL
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: The risk of renal insufficiency in dehydrated children	
Evidence for linking the risk to the medicine	Since the use of ibuprofen in dehydrated children may lead to the development of renal insufficiency, the risk has been considered as an important one. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk group: dehydrated children/adolescents.
Risk minimisation measures	Risk minimization measures are addressed in the relevant section of the SmPC (4.4) and PIL
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: Hematological disorders	
Evidence for linking the risk to the medicine	Hematological disorders such as thrombocytopenia, agranulocytosis, anaemia have been reported with ibuprofen and may be life-thretening if not managed appropriately. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Patients concomitantly on zidovudine may have additional risk.
Risk minimisation measures	Risk minimization measures are addressed in the relevant section of the SmPC (4.8) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important identified risk: High dose and long term treatment	
Evidence for linking the risk to the medicine	Clinical studies suggest that the use of ibuprofen at a high dose may be associated with a small increased risk of arterial thrombotic event. See paragraph Cardiovascular and cerebrovascular disorders above. Risks of long-term use of analgesic are headache and analgesic nephropathy. Risk aligned with the list of safety concerns published by the

	CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Patients on high ibuprofen dose, or with a long-term use of analgesics.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.2 and 4.4) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important potential risk: Use in patients concomitantly on acetylsalicylic acid	
Evidence for linking the risk to the medicine	The possibility that regular, long term use of ibuprofen may reduce cardioprotective effect of low dose acetylsalicylic acid cannot be excluded. These could be potentially serious for the patient. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk group: patients concomitantly on acetylsalicylic acid.
Risk minimisation measures	Risk minimization measures are addressed in the relevant sections of the SmPC (4.5 and 5.1) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important potential risk: Influence of the NSAIDs on the deterioration of the course of infections	
Evidence for linking the risk to the medicine	Ibuprofen may mask the objective and subjective signs of an infection such as fever or pain possibly causing an exacerbation (e.g. development of necrotizing fasciitis). These reactions may have a serious impact on the patient and may require medical care. Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk group: patients with a pre-existining infection.
Risk minimisation measures	Risk minimization measures are addressed in the relevant section of the SmPC (4.4) and PIL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important potential risk: Use in early pregnancy	
Evidence for linking the risk to the medicine	Epidemiological and pre-clinical data suggest dose-and time-dependent negative effects on pregnancy (abortion and malformations). Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk group: pregnant patients at the first or second trimester.
Risk minimisation measures	Risk minimization measures are addressed in the relevant section of the SmPC (4.6) and PIL
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important potential risk: Off-label use	
Evidence for linking the risk to the medicine	A risk of off-label use in patients below 12-year-old, although considered low, cannot be excluded. Children with severe dehydration have an additional risk to develop renal failure. See paragraph relating to the risk of renal insufficiency in dehydrated children.

	Risk aligned with the list of safety concerns published by the CMDh (www.hma.eu/464.html).
Risk factors and risk groups	Risk group: children below 12-year-old.
Risk minimisation measures	Risk minimization measures are addressed in the relevant section of the SmPC (4.2) and PIL
Additional pharmacovigilance activities	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 Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen.

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

There are no studies required for Espidifen, Espididol, Spedifen, Zafen, Spidifen, Spididol, Spididol analgesico, Faspic and Spifen.