Safety concern	Routine risk minimization activities	Additional risk minimization activities
anaphylactic shock	reactions or hypersensitivity to any excipient. • **Section 11** "Adverse reactions" lists the anaphylactic shock, angioedema and hypersensitivity reactions.	
Worsening of pre-existing renal insufficiency	CCDS(Sections 3.2, 6,and 11) • **Section 6** "Precautions" informs on caution to use in case of reduced renal function. • **Section 11** "Adverse reactions" worsening renal insufficiency.	None
Teratogenicity (fetal/neonatal toxicity)	CCDS(Sections 4 and 8) • **Section 4** "Contraindications" describes that the product should not be used during the third trimester of pregnancy. • **Section 8** "Pregnancy" recommends to avoid using ketoprofen during the 1st and 2nd trimesters for lack of information and inform on the risks for the foetus in case of use during the 3rd trimester.	None
Missing Information		
Use in lactation	CCDS (Section: 9) • **Section 9** "Lactation" does not recommend the use during breastfeeding for lack of data.	None
Use in children	CCDS (Section :3.2) • **Section 3** "Dosage and administration" and sub section 3.2 "Special population" reports that pediatric safety and efficacy data are available.	None

DHPC - Direct Healthcare Professional Communication CCDS – Company core data sheet UV – Ultraviolet; ; PIL – Patient Information Leaflet; SmPC – Summary of Product Characteristics; NCA – National Competent Authority.

VI.2. ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1. Overview of disease epidemiology

Musculoskeletal pain

Musculoskeletal pain is the most common cause of severe long-term pain and physical disability, and it affect between 13.5% and 47% of the general population, with a percentage of chronic widespread pain varying between 11.4% and 24 (1), (2). Females are affected more often than males. Although all ages are affected, the peak percentage appears to be among those in the age group 50-74 years (1). The overall percentage of neck pain in the general population ranged between 0.4% and 86.8% while the mean overall percentage was 27.2% in females and 17.4% in males (3).For 2010, low back pain ranked the sixth leading contributor to overall disease burden (4).

Musculoskeletal conditions: Tendonitis, sprain and strain

Tendon injuries are widespread in the general adult population. They are more common among people whose occupations or recreational athletic activities require repetitive motion of the shoulder, knee, elbow, or ankle joints. Women are at greater risk than men for injuries to the tendons (5). Sprains and strains accounted for nearly 18.4 million musculoskeletal injury treatment episodes in 2006/2007, with 7.5 million treated in persons aged 18 to 44, the most common age range in which a sprain or strain is reported and treated.

VI.2.2. Summary of treatment benefits

Topical ketoprofen demonstrated to be effective in the symptomatic treatment of pain associated with muscle and joint injuries (such as contusions, sprains, and tendinitis) or with osteoarthritis.

VI.2.3. Unknowns relating to treatment benefits

The safety and efficacy of ketoprofen gel in children have not been established.

VI.2.4. Summary of safety concerns

Table 4 - Important identified risks

Risk	What is known	Preventability
Skin reaction to a medicine following exposure to sunlight [Photosensitivity skin reactions]	Photosensitivity is a reaction that can be toxic or allergic in nature. No life-threatening or fatal cases have been reported to the Drug safety surveillance database. Patients with history of allergies to other NSAIDs are at higher risk of developing this reaction. Concurrent use of octocrylene (product used in several sunscreen products and other cosmetic products) may increase the risk of photosensitivity reactions. Sun exposure and prolonged treatment with topical ketoprofen can also increase the risks of developing this event.	Patients should protect the treated region with clothing when outdoor, even in the absence of direct sun during treatment with the product and for 2 weeks following its discontinuation to avoid the risk of photosensitization (occurrence of a skin reaction following exposure to sunlight). The gel must not be used with occlusive dressings, and careful and prolonged hand washing should be carried out after each use of the gel. Hands should be washed thoroughly after each application of the ketoprofen gel; the recommended length of treatment should not be exceeded (maximum 7 days of application) to avoid the risk of photosensitization.
Severe allergic reaction including rapid swelling of your lips, face, throat or tongue (angioedema) and potentially fatal wheezing or difficulty breathing **[Severe allergic reactions including angioedema**	Severe allergic reactions have been reported with the use of this product. Ketoprofen topical application can provoke asthma in predisposed subjects. Even topical formulations of NSAIDs should be avoided in patients with a history of asthma following treatment with pain reliever medicines. Patients with known allergic reactions (such as symptoms of asthma, allergic rhinitis or urticaria) to ketoprofen, acetylsalicylic acid, fenofibrate, tiaprofenic	Avoid use in patient with history of hypersensitivity to ketoprofen or to any of the excipients, and in patients with known hypersensitivity reactions to ketoprofen, acetylsalicylic acid, fenofibrate, tiaprofenic acid, or other NSAIDs.

and anaphylactic shock]	acid, or other NSAIDs should not use ketoprofen topical formulation.	
Aggravation of a pre-existing renal failure **[Worsening of pre-existing renal insufficiency]**	Renal impairment is a reaction seen within the group of NSAIDs. Isolated cases of severe systemic adverse reactions including impairment of the renal function have been reported also with the use of topical ketoprofen.	In patients with renal impairment, caution is required since the use of NSAIDs may result in deterioration of renal function.
Risk of congenital anomalies for babies **[Teratogenicity (fetal/neonatal toxicity)]**	This is a reaction seen within the same group of NSAIDs. Risk of fetal toxicities, risk of prolonged duration of bleeding for mother and neonate. May result in fetal toxicities, and may result in sequelae such as cardiopulmonary and renal issues.	Prevent the use during the third trimester of pregnancy.

NSAIDs – Non-Steroidal Anti-inflammatory Drugs

Table 5 - Missing information

Risk	What is known
Limited information on use in breastfeeding women **[Use during lactation]**	No data is available on excretion of ketoprofen in human milk, therefore topical ketoprofen is not recommended in nursing mothers.
Limited information on use in children **[Use in children]**	Topical ketoprofen is not recommended in children since its safety and efficacy has not been established in this category of patients.

VI.2.5. Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

In addition, ketoprofen has special conditions and restrictions for its safe and effective use (additional risk minimization measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in the Human MRIndex of the head of medicines agency website and relevant national competent authorities websites; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities. These additional risk minimization measures are for the following risk:

Table 6 - Summary of additional risk minimization activities by safety concern

Photosensitivity skin reactions	
Risk minimization measure	Risk communication around risk of photosensitivity skin reactions via a yearly DHPC dispatched before the summer period.
Objective and rationale	To maintain the awareness of the healthcare professionals concerning the risk of photosensitivity skin reaction.
Main additional risk minimization measures (key points)	DHPC Optional additional tools to be decided at the country level if suitable, such as: • Target communication to learned societies or in scientific journals. • Prescribers checklist. • Patient information provided through pharmacists and published on NCA website.

DHPC - Direct Healthcare Professional Communication; NCA – National Competent Authority.

VI.2.6. Planned post authorization development plan

Table 7 - List of studies in post-authorization development plan

Study/activity type, tittle and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Joint PASS with a first phase (Pilot study) to evaluate the feasibility of the PASS (Category 3)	Pilot Study: • To assess the prevalence of exposure to topical NSAIDs in a sample of hospital control. • To develop diagnostic criteria for severe photosensitivity. • To obtain estimates of the incidence of severe photosensitivity leading to hospitalization in selected sampling areas.	Photosensitivity skin reactions	Completed	Nov-2013
	PASS: • To evaluate the risk of severe photosensitivity reactions leading to hospitalization in association with the use of topical ketoprofen. • To estimate the crude incidence of severe photosensitivity reactions leading to hospitalization. • To evaluate management		Not started because not feasible according to pilot study results.	Not applicable

	and long-term persistent outcomes of patients having a severe photosensitivity reaction leading to hospitalization.	

PASS: Post–Authorization Safety Studies; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

VI.2.7. Summary of changes to the RMP over time

Not applicable as this is an initial version.