6. PART VI – SUMMARY OF THE RMP

6.1 Overview of disease epidemiology

6.1.1 Pain

Pain is a common complaint among adults, with almost one-fifth reporting general pain, one-third shoulder pain, and up to one-half reporting lower back pain.[2] Acute pain (pain starting suddenly and for shorter duration of time) is the most common symptom for which patients seek medical care. More than half of cases of long standing pain is related to pain of muscles, bones and joints.[3] Approximately, 10% of the general population in the Western suffers from chronic pain of muscles, bones and joints, and is frequent among women as compared with men.[4]

6.2 Summary of existing efficacy data

6.2.1 Pain

Ibuprofen was the first approved pain killer to be sold without doctor's prescription.[5] Ibuprofen in lower doses (200-400 mg/day) is as effective as aspirin in moderate pain but superior to aspirin or paracetamol in pain of teeth.[6] Higher doses (1,800-2,400 mg/day) are used in more severe conditions involving muscles, bones and joints.[7] Ibuprofen is as or more effective than paracetamol for the treatment of pain and fever in adult and children populations.[8]

6.3 Summary of safety concerns

The common side effects are related to digestive system which include indigestion, diarrhea, stomach and / bowel bleeding (vomiting of blood, and black colored stools due to blood in stools), abdominal pain, flatulence, nausea, vomiting, constipation, cramps in stomach. There may be open sores in the lining of stomach and / or bowel and bleeding from stomach or bowel, which can be fatal, especially in the elderly. The other common side effects include mild and transient headache, dizziness, ringing in the ears, and increased urea concentration in blood, increased blood creatinine levels, rashes, and weakness. A full list of all side effects reported with ibuprofen is presented in the SPC and the package leaflet.

The following table provides information on the important identified risks and their preventability:

Identified Risk	What is Known	Preventability
Effects on digestive system (Gastrointestinal effects)	Ibuprofen can cause bleeding, ulcers or holes (perforations) in the stomach and intestines that can lead to death. The chances of bleeding or perforations are higher:	Ibuprofen should not be taken in patients who have ulcers and bleeding from the stomach or bowel.

	• With increasing doses of painkillers (NSAIDs) (Ibuprofen is a type of NSAID) • In patients with a history of ulcers, especially when there is bleeding or perforation and in the elderly patients)	Ibuprofen should also not be taken by patients who have ulcerative colitis (a disease of the large intestine), Crohn's disease, or ulcers in the stomach or bleeding more than once. Patients should stop taking ibuprofen and contact their doctors if they experience pain in the upper part of the stomach and/or bleeding from the stomach or bowel while taking ibuprofen. The patients should also inform their doctors if they have or have had ulcerative colitis or Crohn's disease.
Effects on heart and brain (Cardiovascular and cerebrovascular effects)	Increased blood pressure and fluid retention in the body have been reported in association with NSAID therapy. Use of ibuprofen might be associated with a slightly higher risk of heart attack and stroke (condition that occurs when the blood supply to part of the brain is cut off). The risk is increased when ibuprofen is used for prolonged periods or used at higher doses.	Ibuprofen should not be taken by patients with severe heart failure. The patient should consult doctor if he/she has heart problems, previous history of stroke or are at high risk for this (for e.g. if he/she has high blood pressure, diabetes, high cholesterol or is a smoker). The recommended dose for treatment should not normally be exceeded.
Effects on kidney (Renal effects)	Use of NSAIDs may result in deterioration of kidney function. Those with greatest risk are: • Impaired kidney function patients • Heart failure patients • Impaired liver function patients • Patients treated with water pills (diuretics) • Patients treated with blood pressure lowering medication (angiotensin converting enzyme	The patient should inform his doctor about heart problems or kidney problems or about concomitant use of medicines such as water pills or blood pressure lowering drugs. Ibuprofen should not be taken by patients with severe kidney impairment.

	inhibitors) • Elderly patients Long term treatment with ibuprofen results in pathological changes in the kidney.	
Liver impairment (Hepatic impairment)	Ibuprofen should be used with caution in patients with impaired liver function, because liver toxicity can occur.	Ibuprofen should not be used in patients with severe liver impairment
Increased bleeding (Bleeding disorder)	Ibuprofen like other NSAIDs, prevent blood clotting and has been shown to prolong bleeding time in normal individuals.	Ibuprofen should not be used in patients with severe reduction in platelet counts or who are taking blood thinning agents.
Use in asthmatic and aspirin or other NSAID sensitive patients	Ibuprofen can cause bronchospasm in asthmatic patients (condition that can cause a cough, wheezing and breathlessness)	Ibuprofen should not be given to patients with history of any allergy to aspirin or other NSAIDs.
Concomitant use with other NSAIDs	Co-administration of ibuprofen with other NSAIDs, especially aspirin increases the risk of side effects. In addition, ibuprofen inhibits the blood thinning effect of low dose aspirin.	The patient should inform his doctor before starting the treatment with ibuprofen, if aspirin is concomitantly used.
Use in pregnancy and in women during age of fertility, wishing to become pregnant	Ibuprofen, if administered to pregnant women during the last three months of pregnancy may expose foetus to heart and lung toxicity and kidney dysfunction. The use of ibuprofen may reduce fertility and therefore should not be used in women who want to conceive.	Ibuprofen should not be given to women during the last three months of pregnancy. In the first 6 months of pregnancy, it should be used only if clearly needed and the dose should be kept as low and duration of treatment as short as possible. For women who have trouble conceiving or are undergoing investigation of infertility, withdrawal of ibuprofen should be considered. Ibuprofen should not be used in women who want to become pregnant as it can reduce fertility. If treatment

		with ibuprofen is required, it should be short and with lowest dose possible.

The following table provides important potential risk with the drug product:

Potential Risk	**What is Known**	**Preventability**
Skin effects	Serious skin reactions, some of them leading to death have been reported very rarely in association with the use of NSAIDs. The risk of such reactions appears to be highest early in the treatment. The patient should stop the treatment and contact his doctor immediately if he or she develops a rash, bleeding from linings of stomach or bowel or other allergic reactions	The patient should stop the treatment and contact his doctor immediately if he or she develops a rash, bleeding from mucous membranes or other allergic reactions.

The following table provides important missing information with the drug product:

Important Missing Information	**What is Known**
Use during lactation	Ibuprofen can be used during lactation. However, there should be risk/benefit assessment because infants and children are particularly sensitive to ibuprofen effect.
Use in children < 15 years	Children are particularly sensitive to ibuprofen effect. Hence ibuprofen should not be used in children under 15 years.
Long term use	Long-term treatment with ibuprofen may result in worsening of the pre-existing headache or more frequent attacks of headaches. If this condition develops or is suspected, the patient should seek medical attention for stopping the treatment.

6.4 Summary of risk minimisation activities by safety concern

Routine risk minimisation is provided through the SPC and the Patient Information Leaflet. The SPC of Ibupama tablets is consistent with that of the reference medicinal product.

Routine pharmacovigilance activities are sufficient to identify the actual and potential risks of ibuprofen and no additional post authorization safety studies or risk minimization measures are required.

6.5 Summary of changes to the risk management plan over time

This is the first risk management plan for Ibupama 200 mg film coated tablets.