VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acute pain usually responds to medication and should settle in less than three months. Inadequate pain relief may lead to other complications such as increased blood coagulation, impaired immunity, infections, and others. Inadequately controlled acute pain can be a factor in the development of chronic pain, extended hospital stay, readmission, and patient dissatisfaction.
Acute pain accounts for a plethora of in-patients visits as in the United States of America in 2006, pain was a frequent complaint amongst emergency department visits and pain severity was reported as moderate to severe by 45% of patients in the emergency room. Acute pain is successfully treated with paracetamol, non-steroidal anti-inflammatory drugs, aspirin, or opioid analgesics such as hydrocodone, codeine, tramadol, morphine etc. (41)

Fever is a marker for disease activity in many infectious and inflammatory disorders (reactions include swelling, pain, redness and heat). Fever can also be a response to trauma and injury. Patients with the highest fever tend to have the highest mortality (death) rate. Unfortunately, studies involving people with fever are completely uncontrolled. The antipyretics (medicine that reduces fever) in common use today include paracetamol, acetylsalicylic acid (aspirin) and other NSAIDs. However, antipyretics, by reducing fever, may hide the usual signs of infection.

VI.2.2 Summary of treatment benefits

When it comes to pain intensity and the need for more painkillers, studies with paracetamol/NSAID combinations versus paracetamol, or other NSAIDs have shown that the combination of paracetamol and NSAID was more effective than paracetamol or NSAID alone in 85% and 64% of studies. The pain intensity and the need for extra painkillers was less for both the combination versus paracetamol group and the combination versus NSAID group. Thus, current evidence suggests that a combination of paracetamol and NSAID may offer superior relief of pain than either drug alone.
In a review of studies on the effects of paracetamol, NSAIDs or their combination in management of pain after operation, it was concluded that it may be appropriate to combine the two drugs, as the combination can give additional effect on pain relief compared with either drug alone. However, many of these studies included fewer than 100 patients and they covered a range of surgical indications [37].

VI.2.3 Unknowns relating to treatment benefits

According to the SmPC, there is limited information regarding paracetamol/ibuprofen use in pregnancy, bread-feeding, hepatic impairment, renal impairment, children below age of 12, etc.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reactions, including in patients with asthma (Hypersensitivity and severe skin reactions including anaphylactic reactions and bronchospasm in patients with asthma).	Allergic reactions have been reported with both active ingredients. These range from mild reactions such as skin eruptions, to life-threatening events. Patients diagnosed with asthma, urticaria and other allergies after taking NSAIDs or aspirin are more predisposed to skin reactions or respiratory manifestations when	Patients with previous allergic reactions to either component of the product should not be administered this product. Patients who have experienced asthma attacks or other allergic reactions following administration of ibuprofen or aspirin should not take this medicinal product.

Risk	What is known	Preventability
	administered paracetamol/ibuprofen.	
Liver damage (Hepatotoxicity)	Both active drugs have been reported to cause liver damage and even liver failure, especially paracetamol. In severe poisoning with paracetamol, liver failure may proceed to brain disease, coma and death. Severe liver reactions, including yellowing of the skin or whites of the eyes and cases of fatal inflammation of the liver, though rare, have been reported with ibuprofen as with other anti-inflammatory medication.	Yes, by avoiding intake of paracetamol above the daily recommended dose. Patients should be advised not to take other paracetamol containing or ibuprofen containing products concurrently. Patients diagnosed with liver dysfunction should be observed closely by the prescriber on long term treatment with the medicinal treatment.
Stomach ulcers and bleeding (Peptic ulceration and gastrointestinal bleeding)	Stomach ulcers, bleeding or perforation have been described with anti-inflammatory drugs. The risks increase with dose and duration of treatment, and are more common in patients over the age of 65 years. Some patients will experience indigestion, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when this product is used at the prescribed dose for a few days. The product should be discontinued if there is any evidence of bleeding from the stomach.	Yes, products containing ibuprofen should not be used in patients with a history of stomach bleeding or ulcer since their condition may be worsened.
Kidney damage (Nephrotoxicity)	The medicinal product should be administered carefully in patients with impaired kidney function or kidney disease. Patients with renal disorders and undergoing treatment with the medicinal product should be closely observed by the doctor. The use of the medicinal product with other medications can worsen renal function. These include certain medications used to treat high blood pressure, certain anti-inflammatory drugs such as corticosteroids, certain analgesics, and drugs that suppress the immune response such as ciclosporin, tacrolimus and methotrexate.	Yes, the dose should be kept as low as possible and kidney function should be monitored in patients with kidney impairment, liver impairment or impairment related to the heart.

Risk	What is known	Preventability
	This medicinal product is not indicated in patients with severe liver disease.	
High blood pressure (Hypertension)	The medicinal product can cause high blood pressure or worsen pre-existing high blood pressure. The product should be given with care in patients diagnosed with hypertension (high blood pressure).	Blood pressure should be monitored upon starting treatment and at regular intervals thereafter
Cardiac, cardiovascular and cerebrovascular effects	The use of the medication can predispose to heart attacks or stroke especially when administered at high doses and for a long time. Patients at risk include those already diagnosed with heart or vascular disease.	The product should not be used in patients with heart failure or bleeding in the brain. The medicinal product should be used at the lowest effective dose and for the shortest duration of time.
Severe acute deficiency in blood cells such as neutrophils, platelets etc. (Agranulocytosis and other blood dyscrasia).	The product can cause lower than normal levels of certain blood cells such as neutrophils or platelets causing susceptibility to infection or a tendency to bleed.	The product should not be administered to patients with bleeding disorders.
Interaction with other pain-killers, namely non-steroidal anti-inflammatory agents (Interaction with other NSAIDs)	The medicinal product should not be given altogether with medication of the same pharmaceutical class due to increased risk of adverse drug reactions, especially bleeding and gastro-intestinal reactions.	Patients should not take the product with other non-steroidal anti-inflammatory drugs.
Use of the product together with medicine for lowering the blood pressure (Concomitant administration of antihypertensives (e.g., ACE inhibitors, beta-blockers and diuretics))	The use of drugs for lowering blood pressure (an ACE inhibiting drug and a thiazide diuretic) and an anti-inflammatory drug such as ibuprofen at the same time increases the risk of kidney impairment. The combination of drugs from these three classes should be used with care particularly in elderly patients or those with pre-existing kidney impairment.	Yes, combined use of these medications should be accompanied by close observation/monitoring of renal function.
Interaction with methotrexate leading to increased methotrexate toxicity.	Administration of the medicinal product with methotrexate, a medication employed in the treatment of rheumatoid arthritis may lead to increased methotrexate accumulation within the body and increased toxicity.	Patients should not take both medications at the same time.
Interaction with lithium leading to increased lithium toxicity	Administration of the medicinal product with lithium, a medication employed in the treatment of certain nervous system disorders may lead	Patients should not take both medications simultaneously.

Risk	What is known	Preventability
	to increased lithium accumulation within the body and increased toxicity.	
Interaction with certain prescription medication such as some blood thinning medication (anticoagulant or antiplatelet medication) , anti-inflammatory agents known as corticosteroids or drugs to treat depression (SSRIs) leading to increased risk of bleeding	The product may interact with certain prescription medication such as some blood thinning medication, anti-inflammatory agents known as corticosteroids or drugs to treat depression leading to increased risk of bleeding.	Patients should be monitored if also undergoing treatment with corticosteroids, anticoagulants, certain antidepressants or antiplatelet medication is considered absolutely necessary.
Use during the third trimester of pregnancy	The use of the medicinal product is not indicated during the third trimester of pregnancy due to possible undesirable side effects to the mother and the offspring.	Pregnant women should not takethis medicine during the third trimester of pregnancy.
Inflammation of the brain lining, especially in patients diagnosed with lupus or connective tissue disease (Aseptic meningitis in patients with systemic lupus erythematosus or other connective tissue disorders)	In very rare case, the product may cause inflammation of the brain lining in a narrow group of patients, namely those diagnosed with lupus or other connective tissue disease.	Patients with these conditions must report symptoms such as depression, inability to sleep, confusion, somnolence and fever while treated with paracetamol/ibuprofen.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Off label use in children less than 18 years of age	Effects of the medicinal product in children younger than 18 years of age have not been studied. The outcomes of such therapy are unknown, therefore it is not recommended to be used in this paediatric population.
Impairment of female fertility	The product may impair fertility in women of child bearing age. The product may interfere with fertility investigations or fertility treatments.

Missing information

Risk	What is known
Safety during the first six months of pregnancy and breastfeeding	Effects of paracetamol/ibuprofen have not been studied in the first two trimesters of pregnancy and breastfeeding thus the medicinal product is not recommended in this special population.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines 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 (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for paracetamol/ibuprofen.

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
1.0	06-02-2014	**Identified risks:** • Hepatotoxicity at high doses • Nephrotoxicity • Concomitant administration of antihypertensives (e.g., ACE inhibitors, beta-blockers and diuretics) • Prolonged bleeding time • Peptic ulceration and gastrointestinal bleeding • Severe skin reactions • Medication overuse headache **Potential risks:** • Cardiovascular thrombotic events **Missing information:** • Off label use in children younger than 12 years	
1.1	28-08-2014	**Identified risks:** • Hepatotoxicity at high doses • Nephrotoxicity • Concomitant administration of antihypertensives (e.g., ACE inhibitors, beta-blockers and diuretics) • Prolonged bleeding time • Peptic ulceration and gastrointestinal bleeding • Severe skin reactions • Medication overuse headache	Some administrative changes made to version number 1.1. Procedure number UK/H/5679/01/DC has been excluded.

Version	Date	Safety Concerns	Comment
		Potential risks: • Cardiovascular thrombotic events **Missing information:** • Off label use in children younger than 12 years	
2.0		**Important identified risks:** • Hypersensitivity and severe skin reactions including anaphylactic reactions and bronchospasm in patients with asthma. • Hepatotoxicity • Peptic ulceration and gastrointestinal bleeding • Nephrotoxicity • Hypertension • Cardiac, cardiovascular and cerebrovascular effects • Agranulocytosis and other blood dyscrasia • Interactions with other NSAIDs • Concomitant administration of antihypertensives (e.g., ACE inhibitors, beta-blockers and diuretics) • Interaction with methotrexate leading to increased methotrexate toxicity • Interaction with lithium leading to increased lithium toxicity • Interaction with medication that increase the risk of bleeding and ulceration such as corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) or antiplatelet agents such as aspirin. • Use during the third trimester of pregnancy (including the risk of premature closure of the foetal ductus arteriosus) • Aseptic meningitis (especially in patients with systemic lupus erythematosus or other connective tissue disorders) **Important potential risks:** • Impairment of female fertility • Off-label use in children less than 18 years of age **Missing information:** • Safety during the first six months of pregnancy and breastfeeding	Safety updates following receipt of the Day 70 PrAR from the MHRA and Day 100 Comments received from Sweden

Version	Date	Safety Concerns	Comment
3.0	22-06-2015	No changes	Lay language section updated as requested by the assessor PI updates rendered consequential changes throughout the RMP