PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

IBUPROFEN ORION 200 MG, 400MG AND 600 MG FILM-COATED TABLETS

ORION CORPORATION

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VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Ibuprofen Orion 200mg and 400mg are indicated for short term treatment of mild to moderate pain such as headache (including migraine), period pain (dysmenorrhea), dental pain and fever and pain in common cold in adults and adolescents (12-18 years old).

Ibuprofen Orion 200mg is indicated for children 6-12 years for short term treatment of mild to moderate pain such as headache (including migraine), dental pain, and fever and pain in common cold.

Ibuprofen Orion 400 mg and 600 mg are indicated for symptomatic treatment of pain and inflammation in rheumatic conditions (e.g. rheumatoid arthritis and osteoarthritis), and in painful swelling and inflammation after soft tissue injuries.

Pain is a complex biological phenomena that can be caused by multiple diseases and conditions. More than 1.5 billion people worldwide suffer from chronic pain.[1] Chronic pain of moderate to severe intensity occurs in 19% of adults in Europe.[2] According to a survey report including 5 European countries (United Kingdom, France, Spain, Germany and Italy) approximately 49.7 million people reported pain by both its severity and frequency. Of these, 11.2 million reported severe pain, 29.4 million reported moderate pain and 9.0 million reported mild pain.[3]

A fever is a body temperature that is higher than normal. Fever is a way of the body to react to some abnormal situations, most often infections. It is part of the body's defence against infection. Most bacteria and viruses that cause infections do well at the body's normal temperature but a slight fever can make it harder for them to survive. Fever also activates the immune system. Infections cause most fevers but there can be many other causes, such as medicines, cancers and autoimmune diseases.

The exact prevalences of pain and fever are difficult to assess but they are very common symptoms and sometimes interrelated, as well as associated with inflammation.

Rheumatoid arthritis in the most common inflammatory disease of the joints. The incidence and prevalence of rheumatoid arthritis is suggested to vary between different populations even within the same country; the annual incidence rate of rheumatoid arthritis varies between 20 and 50 cases per 100,000 in Northern European countries.[4]

Osteoarthritis is the most common form of arthritis, where the protective cartilage on the ends of bones wears down over time. It is estimated that 1 in 10 of the population in Europe who are 60 years or older have significant clinical problems that can be attributed to osteoarthritis. The incidence of

osteoarthritis rises steeply in both males and females after the age of 50, peaking in the 70-79 age group.[4]

VI.2.2 Summary of treatment benefits

Pain can be harmful or even restricting for the patient. Pain decreases the quality of life of a patient and can also restrict her/his ability to work. Thus, appropriate and effective treatment of pain is important. Prolonged high fever can be harmful for the body and in those cases it is important to lower the fever.

The active substance in Ibuprofen Orion is ibuprofen, which inhibits the formation of substances that mediate pain, inflammation and fever in the body. Therefore, many symptoms can be treated simultaneously by ibuprofen.

As ibuprofen tablets themselves can cause adverse effects, treatment should optimally be only over the short-term and in the lowest doses that are effective.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Bleeding, ulceration and perforation in stomach and intestines	It is known that the use of Ibuprofen may cause ulcer and bleeding in stomach or intestines. This can sometimes be fatal. Patients with increased risk of ulcer and bleeding are elderly patients, patients with a history of ulcer and patients who are using ibuprofen with high doses and for a long time.	Patients with conditions involving an increased risk for bleeding, and patients with gastrointestinal bleeding or perforation in connection with previous treatment with medications used to relief pain and inflammation (NSAIDs), should not use Ibuprofen Orion. Patients, especially those with high risk of ulcer and bleeding, should be treated with the lowest possible dose. Concomitant use of protective medication should be considered. Patients with high risk of ulcer and bleeding should be monitored closely, particularly in the initial stages of treatment, so that ulcer or bleeding is detected as early as possible. Additionally, treatment with ibuprofen should be stopped if bleeding in

Risk	What is known	Preventability
		stomach or intestines occurs during the treatment.
Adverse effects in heart and blood vessels	The use of ibuprofen, particularly at a high dose (>2400 mg daily) and in long-term treatment can be associated with a small increased risk of myocardial infarction or stroke. In patients with a history of increased blood pressure, impaired function of the heart or other heart-related diseases there is a risk for adverse effects of the heart and/or blood vessels with the use of ibuprofen. Other risk factors include abnormally elevated levels of lipids in the blood, diabetes mellitus and smoking.	Patients with severe heart failure should not use Ibuprofen Orion. Patients with risk factors for adverse effects in heart and/or blood vessels should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment of patients with predisposing risk factors. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary.
Hypersensitivity and allergic reactions	Patients who are allergic to ibuprofen or to any of the excipients may experience allergic reactions when treated with Ibuprofen Orion.	Patients who know that they are allergic to ibuprofen or any of the excipients of the product should not use Ibuprofen Orion. In addition, ibuprofen should not be used in patients who have developed symptoms of asthma, cold-like signs or hives after previous use of aspirin or other NSAIDs.
Impaired renal function	Ibuprofen can decrease the function of the kidneys, especially in patients with renal impairment.	Patients with severe renal impairment should not use ibuprofen. When treating patients with impaired function of the kidneys the dosage of ibuprofen should be assessed individually. The dose should be kept as low as possible and the function of the kidneys should be monitored. Additionally caution should be exercised when Ibuprofen Orion is used in dehydrated children and adolescents due to a risk of renal impairment.
Increased risk of bleeding	Use of ibuprofen can increase the risk of bleeding.	Patients with conditions involving an increased risk for

Risk	What is known	Preventability
		bleeding, and patients with gastrointestinal bleeding or perforation in connection with previous treatment with NSAIDs, should not use Ibuprofen Orion. Patients with a history of a disease in stomach or intestines and patients whose blood does not clot normally should be treated with care and be closely monitored during treatment. The lowest effective dose should be used for the shortest duration necessary to control symptoms.
Aseptic meningitis	Aseptic meningitis (inflammation of the thin tissue that surrounds the brain and spinal cord) has been observed on rare occasions in patients on ibuprofen therapy.	Aseptic meningitis is probably more likely to occur in patients with a certain disorder of the immune system called systemic lupus erythematosus (SLE). Physicians should carefully consider the need for the treatment and monitor these patients closely for symptoms of related diseases.
Use during late pregnancy	When used in the late pregnancy, ibuprofen may cause adverse effects to the foetus, increase the risk of bleeding and prolong labour.	Ibuprofen should not be used during the last trimester of pregnancy.
Use in the elderly	The elderly are at increased risk of serious consequences of adverse reactions, e.g. kidney failure and gastrointestinal bleeding and perforation, which may be fatal.	If ibuprofen treatment is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for bleeding in the stomach and intestines during therapy. In case of impaired renal or hepatic function, the dosage should be individually assessed by the patient´s physician.
Effects in the blood and blood-forming organs (Haematological effects)	Ibuprofen can inhibit platelet aggregation in the blood (platelets clumping together), resulting in prolongation of bleeding time. In very rare	The following patients should not use Ibuprofen Orion: patients who have a current condition or history of a condition involving an increased

Risk	What is known	Preventability
	occasions ibuprofen may affect the formation of blood or blood cells and cause disorders like anaemia (decreased red blood cell count), leucopoenia (decreased white blood cell count), thrombocytopenia (low platelet count), pancytopenia (shortage of all types of blood cells) and agranulocytosis (decrease in the production of granulocytes).	risk for bleeding or perforation in stomach or intestines, patients who have bleeding or perforation in stomach or intestines in connection to previous treatment with ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs) and patients whose blood does not clot normally. Patients with haematological disorders should be treated with care and be closely monitored during ibuprofen treatment, since their condition may be exacerbated. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
Use of high dose (2400 mg) and long-term treatment	Ibuprofen may be associated with a small increased risk of heart attack or stroke, particularly when used at high doses (at or above 2400 mg/day). Long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid. Additionally in long-term treatment ibuprofen may affect hepatic and renal function and cause haematological effects.	Patients should not exceed the recommended dose or duration of treatment. Patients with heart problems including heart failure, angina (chest pain), history of a heart attack, bypass surgery, peripheral artery disease (poor circulation in the legs of feet due to narrow or blocked arteries), any kind of stroke (including 'mini-stroke' or transient ischaemic attack "TIA"), high blood pressure, elevated levels of lipids in the blood or diabetes and patients who are smoking should discuss with his/her doctor or pharmacist before taking Ibuprofen Orion. Adverse events affecting the heart may increase in concomitant use with the following medications: medicines that are anti-coagulants (i.e. thin blood/prevent clotting e.g. aspirin/acetylsalicylic acid, warfarin, ticlopidine) and

Risk	What is known	Preventability
		medicines that reduce high blood pressure (ACE-inhibitors such as captopril, beta-blockers such as atenolol, angiotensin-II receptor antagonists such as losartan). In case of long-term treatment with ibuprofen a periodical monitoring of hepatic and renal function as well as the blood count is necessary, especially in high risk patients.
Use with concomitant non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 enzyme inhibiting drugs (cyclooxygenase-2-selective inhibitors)	The concomitant administration of ibuprofen and other non-steroidal anti-inflammatory drugs, including drugs that inhibit selectively cyclooxygenase-2 enzyme (an enzyme responsible for inflammation and pain) may increase the risk for bleeding in the stomach and intestines.	Concomitant use of other non-steroidal anti-inflammatory drugs and cyclooxygenase-2 enzyme inhibiting drugs (like celecoxib and rofecoxib) should be avoided.
Hepatic impairment in long-term treatment	Ibuprofen may adversely affect the function of the liver, especially in patients with hepatic impairment and especially if used long-term.	Ibuprofen should not be used for patients with severe hepatic failure. Treating patients with mild to moderate hepatic impairment the dose should be kept as low as possible for the shortest duration necessary to control the symptoms and the liver function should be monitored.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Serious skin reactions	The use of Ibuprofen Orion may cause severe, sometimes life-threatening skin reactions, like widespread scaling of the skin (exfoliative dermatitis), skin or mucosal reactions with peeling or

Risk	What is known (Including reason why it is considered a potential risk)
	blistering (e.g. Stevens-Johnson's syndrome). Most these kind of adverse effects occure at the start of the treatment, during the first month.
Use during early pregnancy	Use of ibuprofen during early pregnancy may adversely affect the pregnancy and/or the development of the foetus. During the first and second trimester of pregnancy, ibuprofen should not be used unless clearly necessary. If it is considered necessary, the dose should be as low as possible for the shortest duration necessary to control the symptoms.
Use during breast-feeding	Ibuprofen is excreted in breast milk but with normal doses and short-term use, it is unlikely that it affects the infant. If ibuprofen is prescribed for a long-term treatment, early weaning should be considered.
Masking signs of infection and potential worsening of existing infections	Ibuprofen may cause a reduction in the number of white blood cells and decrease resistance to infection. Existing infections related to skin may develop or become more severe (a condition such as necrotising fasciitis may develop characterized by intense pain, high fever, swollen and hot skin, blistering, necrosis).
Impairment of female fertility	Ibuprofen may impair the fertility in women. This effect is reversible on stopping the medicine. The use of ibuprofen is not recommended while attempting to conceive or during investigation of infertility.

Missing information

Risk	What is known
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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. The Summary of Product Characteristics and the Package leaflet for this medicinal product can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.