PUBLIC SUMMARY OF RISK MANAGEMENT PLAN

BURANA 40 MG/ML ORAL SUSPENSION

DATE: 15-5-2015, VERSION 1

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Musculoskeletal pain:

Musculoskeletal pain affects muscles, bones, tendons etc., and includes arthritis of the joints (e.g. osteoarthritis and rheumatoid arthritis) and low back pain. A 2007 EU survey found that 22% of people had experienced musculoskeletal problems such arthritis (European Commission 2007). Osteoarthritis (OA) is the most common joint disorder affecting 1 in 10 adults above the age of 60 years. The incidence of OA increases with age after 50 years peaking between the ages of 70-79 years (Olivera et al., 1995). The yearly occurrence of RA ranges between 20 and 50 cases per 100,000 population in Northern European countries but may be lower in Southern European countries (Carbonell et al., 2008, Pedersen et al., 2009).

A national survey in the Netherlands revealed that 74.5% of people had experienced musculoskeletal pain in the preceding 12 months (Picavet and Schouten, 2003). Back pain was reported by 44% of people, followed by neck pain (31%), and shoulder pain (30%). Back pain is considered to be the most common type of musculoskeletal pain and may affect up to 50% of adults (McBeth and Jones, 2007).

Non-musculoskeletal pain:

This includes such conditions as headache, migraine and dysmenorrhoea (period pain). From a 2011 national health survey in the USA, migraine or other severe headache occurring within the last 3 months was reported by 16.6% of adults over 18 years of age (Smitherman et al.2013). Headache was most common reported by women aged 18-44 years (26.1%) and men aged 75 years and older were least affected (Smitherman et al., 2013).

Dysmenorrhoea is the most common gynaecological problem in women of all ages and races (Proctor and Farquhar, 2006). Estimates of the prevalence of dysmenorrhea in the population vary widely (16.8% to 81%3), and rates as high as 90% have been documented (Jamieson and Steege, 1996).

Diseases accompanied by fever:

This includes the common cold, influenza (flu) and other infections. Young children and elderly people are at higher risk for getting these viral infections. Also people with weak immune systems, diabetes and certain other diseases such as cancer and chronic bronchitis are more likely to developing serious infections. The incidence of the common cold is five to seven episodes per year in preschool children, and two to three per year by adulthood (Monto 1994).

VI.2.2 Summary of treatment benefits

Ibuprofen belongs to the class of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). It works by blocking an enzyme called cyclooxygenase, which produces prostaglandins, substances

that are involved in producing pain and inflammation. Ibuprofen reduces levels of prostaglandins and is therefore used to treat symptoms of pain, swelling, inflammation and fever which can occur in conditions such as cold/flu, muscular injury and arthritis.

Pinewood does not have access to data from clinical trials on the brand leader, so cannot provide an informed analysis of the treatment benefits. However, Ibuprofen Oral Suspension can be effective in the following indications:

- Children under 12 years

  Ibuprofen 200 mg/5 ml Oral Suspension is indicated for rheumatic or muscular pain, headache, dental pain, feverishness (including post-immunisation pyrexia), symptoms of cold and influenza.

- Over 12 years

Ibuprofen 200 mg/5 ml Oral Suspension is indicated for rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

VI.2.3 Unknowns relating to treatment benefits

Pinewood does not have access to data from clinical trials on the brand leader, so cannot provide an informed analysis of the unknowns relating to treatment benefits. However, there is no evidence currently available to indicate that dosing should be adjusted in elderly patients or in patients of different ethnic groups. The safety and effectiveness of Ibuprofen in children under 3 months of age or weighing less than 5kg have not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Serious gastrointestinal toxicity including bleeding, ulceration or perforation (Effects on the stomach and bowel)	The most common side effects of ibuprofen are stomach problems including nausea, vomiting and tummy pain. Ibuprofen can also cause serious side effects in the stomach or bowel such as ulcers, bleeding or burst (perforated) ulcers. Elderly patients, patients on higher doses of ibuprofen, patients with a past history of ulcers, or those on certain other medications may be more at risk of getting ulcers related to ibuprofen use. Also, patients who take ibuprofen for a longer time may be at higher risk.	By following the special warnings and precautions information set out in the product label, including the guidance to use the lowest ibuprofen dose for the shortest time to relieve symptoms Also, the recommendation to use ibuprofen with caution in patients who have other risk factors for stomach ulcers or bleeding. These include elderly patients, patients with a history of ulcers, and those taking other medications which could cause ulcers (e.g. steroids and aspirin). If such patients require ibuprofen treatment, doctors should also consider starting them on antacid medication to protect the stomach.

Risk	What is known	Preventability
Hypersensitivity reactions including anaphylaxis (Allergic type reactions)	Ibuprofen may cause an allergic (hypersensitivity) reaction in some patients. Patients may get a skin rash, itchy skin, and hives. In rare cases, patients may experience severe allergic reactions to ibuprofen, and develop swelling of their tongue, throat, lips and face, problems with breathing, palpitations (fast heart rate) and a fall in blood pressure which could be life-threatening. Some patients may be more at risk of these side effects, including patients with a history of allergy, eczema, hayfever or asthma.	By following the warnings and precautions information provided in the product label. The label specifies that ibuprofen should not be used in patients who have a known history of sensitivity to ibuprofen, and those with a history of asthma or rash brought on by aspirin, or other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen.
Bronchospasm in patients with a history of bronchial asthma or allergic disease (Narrowing of the lung airways causing breathing difficulties)	Ibuprofen may cause a worsening of asthma in some patients, particularly those who have poorly controlled asthma, or who are sensitive to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). These patients may develop a narrowing of their airways (bronchospasm) and difficulty breathing with cough and wheeze. Ibuprofen works to relieve pain and fever by blocking and enzyme in the body called cyclooxygenase (COX), and thereby reducing the levels of chemicals called prostaglandins in the body. However, by doing this, levels of another chemical called leukotrienes are increased at the same time. It is thought that this increase in the amount of leukotrienes is responsible for producing asthma and allergic effects.	The product label specifies that the use of ibuprofen should be avoided in patients with a history of asthma brought on by aspirin, or other non-steroidal anti-inflammatory drugs (NSAIDs) similar to ibuprofen.Additional warning and precautions related to the risk of asthma attacks brought on by ibuprofen is provided in the product label.
Cardio-renal effects (hypertension, oedema) [High blood pressure and water retention in the body]	Ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) are linked to an increased risk of high blood pressure (hypertension), heart failure and fluid retention in the body. Also, ibuprofen may make blood pressure-lowering medications less effective in treating high blood pressure. Therefore the use of ibuprofen could make high blood pressure worse. High risk patients include those with a previous history of heart failure, patients with high	Special warnings and precautions information is provided in the product label. Caution is advised when using ibuprofen in patients with a history of heart disease, heart failure or kidney (renal) failure.

Risk	What is known	Preventability
	blood pressure, diabetics and elderly patients.	
Use during third trimester of pregnancy (including risk of premature closure of patent ductus arteriosus, delayed labour, increased bleeding tendency)	Ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) may cause damage such as kidney problems in the unborn baby if used during the third trimester of pregnancy. The onset of labour may be delayed and duration of labour increased with an increased risk of bleeding in both mother and child.	Information and warning on ibuprofen exposure in in the later stages of pregnancy is discussed in the product label and patient information leaflet.The product label states that ibuprofen should not be taken in the third trimester of pregnancy.
Hepatic disorders (Abnormal liver function)	Abnormal liver function has been reported very rarely with ibuprofen.	There are warnings and precautions provided in the product label and the patient information leaflet and insert. Caution is advised when using ibuprofen in patient with liver problems, and should not be used in severe liver failure.
Renal disorders (Abnormal kidney function)	Kidney function may get worse as a result of ibuprofen treatment. Ibuprofen works to relieve pain and fever by blocking the cyclooxygenase (COX) enzyme, and reducing the levels of chemicals called prostaglandins in the body. Prostaglandins are thought to play an important role in helping to maintain enough blood flow to the kidneys. Ibuprofen causes a reduction in prostaglandin levels, and therefore kidneys do not receive adequate blood flow and this leads to worsening in the function of the kidneys and possibly reduced production of urine. Ibuprofen may also have a direct toxic damaging effect on the kidneys causing tissue inflammation (nephritis) or tissue destruction (necrosis).	Special warnings and precautions information is provided in the product label. Caution is advised when using ibuprofen in patients with preexisting renal problems. Ibuprofen should not be used in severe renal failure.
Serious skin reactions	Ibuprofen can very rarely cause severe skin reactions which could be life-threatening or even result in death. These skin reactions include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) which present as fever and blistering rash and ulceration affecting the skin, mouth, lips and eyes. Such reactions are thought to arise	Warnings and precautions information about severe skin reactions are set out in the product label.

Risk	What is known	Preventability
	as a result of the activation of the immune system when the patient is exposed to the drug. The risk of severe skin reactions with ibuprofen treatment is higher for older patients, women, and those just beginning treatment. Typically, the symptoms of SJS appear early after commencing treatment, usually within the first month of starting the medication.	
Interactions with anticoagulants, methotrexate, lithium, cardiac glycosides (Drug interactions)	Ibuprofen can interact with a number of different medications and increase the levels of these drugs in the body making them toxic. Also ibuprofen may directly affect how well the blood clots, and this could lead to an increased risk of bleeding when ibuprofen is used together with other drugs which impair blood clotting (anticoagulants) such as warfarin and heparin.	Warnings regarding the interaction between ibuprofen and anticoagulants and antiplatelet drugs are provided in the product label. The drug-drug interaction section 4.5 of the Ibuprofen product label discusses all various medications which could potentially interact with ibuprofen.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Arterial thrombotic events (e.g. myocardial infarction, stroke) [Blood clots resulting in heart attacks, strokes etc.]	Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400mg daily) and in long-term treatment may be associated with a small increased risk of blood clots resulting in, for example, heart attack or stroke. Overall, there is not enough evidence to suggest that low dose ibuprofen (e.g. less than 1200mg daily) is associated with an increased risk of such events. The risks of heart attack and stroke are related to how long ibuprofen is used for and the dosage. High risk patients include those with a history of a previous heart attack, or stroke, elderly people, diabetic patients and smokers.
Impaired female fertility (Reduced ability to conceive)	Ibuprofen works to relieve pain and fever by blocking the cyclooxygenase (COX) enzyme, thereby reducing the synthesis and blood levels of chemicals called prostaglandins in the body. In animals, administration of similar drugs which lower blood levels of prostaglandins has been shown to impair pregnancy and cause miscarriage. Therefore, the use of ibuprofen may reduce fertility and is not recommended in women attempting to conceive.
Increased risk of aseptic meningitis in patients with systemic lupus erythematosus and mixed connective tissue disease (Inflammation of the brain membranes caused by drugs)	Aseptic meningitis is an inflammation of the protective membranes or linings that surround the brain and spinal cord which is not caused by a bacterial or viral infection. Rather the meningitis is related to drug treatment. Drug-induced aseptic meningitis caused by ibuprofen is very rare. It is believed to be linked to the increased immune system sensitivity to ibuprofen (drug hypersensitivity). Drug- induced aseptic meningitis is more common in patients with a history of autoimmune disease,

Risk	What is known (Including reason why it is considered a potential risk)
	particularly systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD)

Missing information

Risk	What is known
Use during 1st and 2nd trimesters of pregnancy	Ibuprofen works to relieve pain and fever by blocking the cyclooxygenase (COX) enzyme, and reducing the production of chemicals called prostaglandins in the body. Epidemiological study data suggests that if similar drugs which prevent prostaglandin production are used in early pregnancy, there is an increased risk of miscarriage as well as heart and bowel defects in the unborn baby. The absolute risk for congenital heart defects was increased from less than 1 %, up to approximately 1.5%.The risk is believed to increase with dose and duration of drug therapy. Also, in animals, administration of drugs which block prostaglandin production has been shown to cause embryo loss, as well as increases in various different organ malformations including heart defects,
Use during breast feeding	In limited studies, ibuprofen appears in breast milk in very low concentration and is unlikely to affect the breast fed infant adversely. However with long term use side effects on the baby cannot be excluded.
Exposure in children below 3 months of age	There is insufficient clinical trial data or experience supporting the safety and effectiveness of ibuprofen in children under 3 months of age.

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 healthcare 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 Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures. The SmPC and the PIL for ibuprofen oral suspension can be found on the Medicines and Health Care Products Regulatory Agency (MHRA) website (www.mhra.gov.uk/spc-pil).

This medicine has no additional risk minimisation measures.

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

There are no planned or ongoing post-authorization safety studies for ibuprofen oral suspension and no ongoing or proposed post-authorization efficacy studies for ibuprofen oral suspension.

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

Since this is the first Risk Management Plan (RMP) for ibuprofen, there are no previous versions of this RMP and thus no summary of changes.