VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Osteoarthritis

Sometimes called degenerative joint disease or degenerative arthritis, osteoarthritis (OA) is the most common chronic condition of the joints. OA can affect any joint, but it occurs most often in knees, hips, lower back and neck, small joints of the fingers and the bases of the thumb and big toe.

In OA, the cartilage, which covers the end of each bone, breaks down, causing pain, swelling and problems moving the joint. OA worsens over time and an inflammatory process occurs and cytokines (proteins) and enzymes develop that further damage the cartilage. In the final stages of OA, the cartilage wears away and bone rubs against bone leading to joint damage and more pain.

Although OA occurs in people of all ages, it is most common in people older than 65. Common risk factors include increasing age, obesity, previous joint injury, overuse of the joint, weak thigh muscles, and genes.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a long-term inflammatory disease of unknown cause. It is thought that the disease may start after an external trigger (eg, cigarette smoking, infection, or trauma) that causes an autoimmune reaction, leading to changes of the joint cavity such as swelling, new fibrous tissue formation and the fusion of affected joints. Because RA also can affect body systems, such as the cardiovascular or respiratory systems, it is called a systemic disease.

Patients with RA may report difficulty performing activities of daily living, such as dressing, standing, walking, personal hygiene, or use of hands. Other symptoms (e.g., fatigue, feeling generally unwell, morning stiffness, weight loss, and mild fever) may be present

Nearly three times as many women have the disease as men. In women, RA most commonly begins between ages 30 and 60. In men, it often occurs later in life. Having a family member with RA increases the odds of having RA; however, the majority of people with RA have no family history of the disease.

Ankylosing spondilytis

Ankylosing spondylitis (AS) is a long-term disorder mainly involving the joints of the hip and spine, although it can also cause other problems such as arthritis, swelling where a tendon or ligament attaches to the bone (enthesitis), and symptoms not involving the joints. The cause of AS is not understood completely; however, a strong genetic link exists. Symptoms of AS include those related to inflammatory back pain, enthesitis and arthritis, and other symptoms not involving the joints. Chronic pain and stiffness are the most common complaints of patients with AS. Fatigue is another common complaint. Most patients report their fatigue to be moderately severe. Increased levels of fatigue are associated with increased pain and stiffness and decreased ability to function. Fever and weight loss may occur during periods of active disease.

The disease is more common in men than in women. Ankylosing spondylitis may develop in childhood, and boys are more likely to have it than girls. This disease occurs more often in Caucasians, Asian and Hispanic populations.

Acute gouty arthritis

Gout is a form of inflammatory arthritis that develops in some people who have high levels of uric acid in the blood. The acid can form needle-like crystals in a joint and cause sudden, severe episodes of pain, tenderness, redness, warmth and swelling.

Acute gout, or a gout attack, happens when something (such as a night of drinking) causes uric acid levels to spike or jostles the crystals that have formed in a joint, triggering the attack. The resulting inflammation and pain usually strike at night and intensify over the next eight to 12 hours. The symptoms ease after a few days and likely go away in a week to 10 days. Some people never

experience a second attack, but an estimated 60% of people who have a gout attack will have a second one within a year. Overall, 84% may have another attack within three years.

Postoperative dental surgery pain
Pain is a major postoperative symptom in many oral surgical procedures. It is a complex and variable phenomenon that can be influenced by many factors. Good management of oral surgical pain requires a detailed understanding of the pathogenesis of surgical pain. Onset of pain usually begins as the effects of the local anesthetic agent subside. Unless treated, moderate to severe pain usually occurs during the first 24 hours, with peak intensity after about 6-8 hours, when a conventional local anesthetic is used.

VI.2.2 Summary of treatment benefits

Etoricoxib is a member of a group of medicines called non-steroidal anti-inflammatory agents (NSAIDS). Etoricoxib is also known as a cyclo-oxygenase-2 (COX-2) inhibitor with a high degree of selectivity for its target because it works by blocking this enzyme in the body. COX-2 is involved in the production of mediators of pain and inflammation in response to disease. By blocking the action of COX-2, etoricoxib reduces pain and inflammation.

In patients with OA, etoricoxib 60 mg once daily reduced pain and improved patients' assessments of disease status. These beneficial effects were observed as early as the second day of therapy and were maintained for up to 52 weeks.

In patients with RA, etoricoxib 90 mg once daily improved pain, inflammation and mobility. These beneficial effects were maintained over the 12-week treatment period.

In patients experiencing acute attacks of gouty arthritis, etoricoxib 120 mg once daily, over an eight-day treatment period, relieved moderate to extreme joint pain and inflammation that was comparable to indomethacin 50 mg three times daily. Pain relief was observed as early as 4 hours after start of treatment.

In patients with AS, etoricoxib 90 mg once daily improved spine pain, inflammation, stiffness and function. The beneficial effects of etoricoxib were observed as early as on the second day of therapy and were maintained throughout the 52-week treatment period.

In a study assessing pain following dental surgery, etoricoxib 90 mg was administered once daily for up to 3 days. In the subgroup of patients with moderate pain at baseline, etoricoxib 90 mg demonstrated a pain-relieving effect similar to that of ibuprofen 600 mg and greater than that of paracetamol/codeine 600 mg/60 mg and placebo as measured by total pain relief over the first 6 hours. Out of every 100 patients treated with the medicines under study, the proportion of patients reporting the use of rescue medicines within the first 24 hours of dosing was 41 for etoricoxib, 25 for ibuprofen, and 47 for paracetamol / codeine compared to 76 for placebo.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about the effectiveness of the drug in the target population were identified, that would warrant further effectiveness studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex and race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Serious gastrointestinal events	***Ulcers in the digestive tract*** are most often associated with the stomach and small intestine. In general, an ulcer is any eroded area of skin or a mucous membrane, marked by tissue disintegration. It can be a painful and dangerous situation. Ulcers are associated not only with pain and discomfort, but may also be a source of significant blood loss. There are many other factors that influence the formation of ulcers. Smoking, poor diets, steroid medication and NSAID medication can all increase ulcer formation. Patients who chronically use anti-inflammatory medication should alert their doctor to any new stomach pains, digestive problems or signs of blood in the stool such as bright, red blood or dark, tarry stools. Like any other COX-2 selective inhibitor, etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces the generation of prostaglandins (PGs) from arachidonic acid. Among the different functions exerted by PGs, their role in the inflammation cascade should be highlighted. COX-2 selective inhibitor (aka "COXIB") showed less marked activity on type 1 cycloxigenase compared to traditional NSAID. This reduced activity is the cause of reduced gastrointestinal toxicity, as demonstrated in several large clinical trials performed with different COXIB. There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib, other selective COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).	Routine pharmacovigilance by monitoring for early symptoms is sufficient. Etoricoxib should not be taken in cases if the patient suffers from a stomach ulcer or bleeding in the stomach or intestines, or the patients have inflammatory bowel disease, such as Crohn's disease, ulcerative colitis, or colitis. Doctor or pharmacist should be informed if the patients have a history of stomach bleeding or ulcers. Doctor or pharmacist should also be informed, if the patients take acetylsalicylic acid, because the risk of stomach ulcers is greater if etoricoxib is taken concomitantly with acetylsalicylic acid. Like all medicines, this medicine can cause side effects, although not everybody gets them.

Thrombotic cardiovascular events	Whether an ischemic stroke (occur as a result of an obstruction within a blood vessel supplying blood to the brain) is due to a noncardiogenic or cardiogenic source, the mechanism of causing a stroke is the same. Both sources are involved with the development of thrombi (intravascular coagulation of the blood in any part of the circulatory system, as in the heart, arteries, veins, or capillaries) that move from their original source to the brain blocking blood flow in the process. ***Cardiovascular events*** refer to any incidents that may cause damage to the heartmuscle. The heart is a busy organ, constantly pumping blood filled with oxygen and nutrients through your arteries, into the heart muscle (myocardium). Any interruption of blood flow will lead to an injury, or infarction. This is called a heart attack, or a myocardial infarction. This is also known as a coronary or cardiovascular event. Clinical trials suggest that the selective COX-2 inhibitor class of medicines (of which etoricoxib is one) may be associated with an increased risk of thrombotic events (especially myocardial infarction and stroke), relative to placebo and some NSAIDs (naproxen).	Routine pharmacovigilance by monitoring for early symptoms is sufficient. Etoricoxib should not be taken in cases if the patients have high blood pressure that has not been controlled by treatment, diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain), have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries) or any kind of stroke (including mini-stroke, transient ischaemic attack or TIA). Etoricoxib may slightly increase a risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke. Doctor or pharmacist should be informed if the patients have a history of heart failure, or any other form of heart disease, or a history of high blood pressure, or diabetes, high cholesterol, or are a smoker. These can increase the risk of heart disease. As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. Patients on long-term treatment should be reviewed regularly, such as every three months, with regards to efficacy, risk factors and ongoing need for treatment. Like all medicines, this medicine can cause side effects, although not everybody gets them.

Renovascular events: oedema, hypertension and congestive herat failure	***Water retention*** or ***edema*** refers to the abnormal collection of water within the tissues of the body. Also known as ***fluid retention***, water retention is commonly noted as puffiness in the feet, ankles and legs. Water retention may be caused due to a wide range of factors. These factors result in increased accumulation of water and other fluids in the spaces between the cells and tissues by altering the mechanism that normally clears excess fluids in these spaces. The body may become congested, and ***congestive heart failure*** is the term used to describe the condition. It is a chronic progressive condition that affects the pumping power of heart muscles. The causes of water retention can be broadly categorized into general causes and pathological causes. The general causes of water retention include gravity, burns, pregnancy, consumption of medications, dietary factors, and menstrual cycle. ***Hypertension*** = ***high blood pressure***, is a condition in which the arteries have persistently elevated blood pressure. As with other medicines known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in some patients taking etoricoxib.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. Etoricoxib should not be taken in cases if the patients have high blood pressure that has not been controlled by treatment, diagnosed heart problems including heart failure (moderate or severe types) or angina (chest pain). The possibility of exacerbating fluid retention, oedema or hypertension should be taken into consideration when etoricoxib is used in patients with swelling due to fluid retention, hypertension, or heart failure. Close monitoring is essential. Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypersensitivity-related events and serious skin reactions	***Hypersensitivity reaction*** refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.The pathophysiology of these reactions with etoricoxib is unknown. Physicians should weigh the potential benefits of prescribing etoricoxib versus the potential risks. ***Skin reactions*** to drug therapy are extremely common. All drugs may induce skin reactions, although if they do occur they are usually mild, however, some skin reactions are serious and potentially life-threatening.Serious skin reactions, some of them fatal, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors. These serious events may occur without warning. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any medicine allergy.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. Etoricoxib should not be taken in cases if the patients are allergic (hypersensitive) to etoricoxib or any of the other ingredients of this medicine, or to NSAIDs, including aspirin and COX-2 inhibitors. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Like all medicines, this medicine can cause side effects, although not everybody gets them.

Missing information

Risk	What is known
Use in pregnancy and lactation	Etoricoxib should not be used in cases if the women are or could be pregnant. It is not known if etoricoxib is excreted in human milk. Women who use etoricoxib must not breast feed. Etoricoxib is not recommended in women attempting to become pregnant.
Use in patients less than 16 years old	Etoricocxib should not be taken by children and adolescents under 16 years of age.
Use in patients with renal insuficiency	Etoricocxib should not be taken in cases of serious kidney disease. Etoricoxib is not recommended in patients with a history of liver or kidney disease.
Use in patients with hepatic impairment	Etoricocxib should not be taken in cases of serious hepatic disease. Etoricoxib is not recommended in patients with a history of liver or kidney disease. In patients with mild liver disease etoricoxib should not be taken more than 60 mg. In patients with moderate liver disease etoricoxib should not

	be taken more than 30 mg.

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

Not applicable. No postauthorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, this is the first Risk management plan.