Elements for a public summary

VI.2.1 Overview of disease epidemiology

Not applicable. Proposed SmPC comply with the innovator's product regarding indications and adverse events.

VI.2.2 Summary of treatment benefits

Not applicable. Proposed SmPC comply with the innovator's product regarding indications and adverse events.

VI.2.3 Unknowns relating to treatment benefits

Not applicable. Proposed SmPC comply with the innovator's product regarding indications and adverse events.

VI.2.4 Summary of safety concerns

Important identified risks		
	What is known	**Preventability**
Cardiovascular thrombotic effects Hypertension	***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. ***Hypertension*** = ***high blood pressure***, is a condition in which the arteries have persistently elevated blood pressure. Celecoxib is classified as selective cyclooxygenase (COX)-2 inhibitor. Other nonsteroidal anti-inflammatory drugs (NSAIDs) effect both COX-1 and COX-2 activity. Chronic use of celecoxib may cause an increased risk of serious	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding cardiovascular thrombotic events and hypertension: ***Do not take <Invented name>*** - if you have heart failure, established ischaemic heart disease, or cerebrovascular disease, e.g. you have been diagnosed with a heart attack, stroke, or transient ischaemic attack (temporary reduction of blood flow to the brain; also known as “mini-stroke”), angina, or blockages of blood vessels to the heart or brain; - if you have or have had problems with your blood circulation (peripheral arterial disease) or if you have had surgery on the arteries of your legs;

	adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can also be fatal. All NSAIDs, both COX-2 selective and non-selective, may have a similar risk of serious adverse cardiovascular thrombotic events. Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur. As with all NSAIDs, celecoxib can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.	***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you smoke, have diabetes, raised blood pressure or raised cholesterol; - if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you; As with other NSAIDs (e.g. ibuprofen or diclofenac) this medicine may lead to an increase in blood pressure, and so your doctor may ask to monitor your blood pressure on a regular basis. ***How to take <Invented name>*** Your doctor will tell you what dose you should take. As the risk of side effects associated with heart problems may increase with dose and duration of use, it is important that you use the lowest dose that controls your pain and you should not take <Invented name> for longer than necessary to control symptoms.
Gastrointestinal ulcer-related 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.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding gastrointestinal ulcer-related events: ***Do not take <Invented name>*** - if you **currently** have an ulcer in your stomach or intestines, or bleeding in your stomach or intestines;

	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. NSAIDs, including celecoxib, can cause serious gastrointestinal (GI) events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be	- if you have an inflammatory disease of the intestines such as ulcerative colitis or Crohn's disease; ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you have **previously** had an ulcer or bleeding in your stomach or intestines. **(Do not take <Invented name>** if you **currently** have an ulcer or bleeding in your stomach or intestine).

	taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during celecoxib therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.	
Renal toxicity	***Renal toxicity*** = ***Nephrotoxicity*** is one of the most common kidney problems and occurs when human body is exposed to a drug or toxin that causes damage to the kidneys. When kidney damage occurs, kidneys are unable to rid the body of excess urine, and wastes. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding renal toxicity: ***Do not take <Invented name>*** - if you have severe kidney disease; ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you; ***How to take <Invented name>*** ***Kidney or liver problems:*** make sure your doctor knows if you have liver or kidney problems as you may need a lower dose.

	state. No information is available from controlled clinical studies regarding the use of celecoxib in patients with advanced renal disease. Therefore, treatment with celecoxib is not recommended in these patients with advanced renal disease. If celecoxib therapy must be initiated, close monitoring of the patient's renal function is advisable.	
Fluid retention and oedema	***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 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. Prolonged consumption of certain medications that belong to the group of anti-hypertensives, corticosteroids and some pain relieving agents (NSAIDs) has been associated with water retention. These medications may alter the normal functioning of the blood vessels to cause water retention. Fluid retention and oedema have been observed in some patients taking NSAIDs, including celecoxib. Celecoxib should be used with caution in patients with	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding fluid retention and oedema: ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you have fluid retention (such as swollen ankles and feet);

	fluid retention or heart failure.	
Hypersensitivity reactions **Severe skin reactions**	***Hypersensitivity reaction*** refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. ***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. ***Hypersensitivity reactions*** As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to celecoxib. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving celecoxib. Celecoxib should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs. ***Skin reactions*** Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding hypersensitivity reaction and severe skin reactions: ***Do not take <Invented name>*** - if you are allergic to celeoxib or any of the other ingredients of this medicine; - if you have had an allergic reaction to a group of medicines called "sulphonamides" (e.g. some antibiotics used to treat infections); - if as a result of taking acetylsalicylic acid or any other anti-inflammatory and pain-relieving medicine (NSAID) you have had asthma, nose polyps, severe nose congestion, or an allergic reaction such as an itchy skin rash, swelling of the face, lips, tongue or throat, breathing difficulties or wheezing; ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you are taking acetylsalicylic acid (even at low dose for heart protective purposes); - if you are using <Invented name> at the same time as other non-acetylsalicylic NSAIDs such as ibuprofen or diclofenac. The use of these medicines together should be avoided; - if you have had a serious allergic reaction or a serious skin reaction to any medicines;

Severe hepatic reactions	***Liver disease*** = ***hepatic disease*** is any disturbance of liver function that causes illness. The liver is responsible for many critical functions within the body and should it become diseased or injured, the loss of those functions can cause significant damage to the body. Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including celecoxib. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), celecoxib should be discontinued.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding severe hepatic reactions: ***Do not take <Invented name>*** - if you have severe liver disease; ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you; Some cases of severe liver reactions, including severe liver inflammation, liver damage, liver failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Of the cases that reported time to onset, most severe liver reactions occurred within one month of start of treatment. ***How to take <Invented name>*** ***Kidney or liver problems:*** make sure your doctor knows if you have liver or kidney problems as you may need a lower dose.

Important identified interactions		
	What is known	**Preventability**
Warfarin and	***Warfarin*** (and also similar agents)	Routine pharmacovigilance by

similar agents – risk of serious bleeding	is an anticoagulant (blood thinner). It reduces the formation of blood clots. Warfarin is used to prevent heart attacks, strokes, and blood clots in veins and arteries. Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily 2-5 mg doses of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin.	monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding interaction with warfarin and similar agents: ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you use medicines to reduce blood clotting (e.g. warfarin) ***Other medicines and <Invented name>*** Some medicines can affect the way other medicines work. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription: - Warfarin or other oral anticoagulants ("blood-thinning" agents that reduce blood clotting)
Lithium – risk of lithium toxicity	***Lithium*** affects the flow of sodium through nerve and muscle cells in the body. Sodium affects excitation or mania. Lithium is used to treat the manic episodes of manic depression. Manic symptoms include hyperactivity, rushed speech, poor judgment, reduced need for sleep, aggression, and anger. It also helps to prevent or lessen the intensity of manic episodes. Celecoxib increases the concentration of lithium in the blood by 17 % and may promote lithium toxicity. Therefore, lithium therapy should be closely monitored during and after therapy with celecoxib.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding interaction with lithium: ***Other medicines and <Invented name>*** Some medicines can affect the way other medicines work. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription: - Lithium (used to treat some types of depression);
ACE-inhibitors	An ***ACE inhibitor*** (or ***angiotensin-***	Routine pharmacovigilance by

and Angiotensin II antagonists, diuretics (furosemide, thiazide) – risk of NSAID induced acute renal failure	***converting-enzyme inhibitor***) is a medication pharmaceutical drug used primarily for the treatment of high blood pressure (hypertension) and weak heart muscle (congestive heart failure). ***Angiotensin II receptor antagonists***, also known as ***angiotensin receptor blockers (ARBs), AT_1-receptor antagonists*** or ***sartans***, are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system. Their main uses are in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure. NSAIDs may diminish the antihypertensive effect of ACE inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE-inhibitors and angiotensin II antagonists. ***Thiazide*** is a type of molecule and a class of diuretics often used to treat hypertension (high blood pressure) and edema (such as that caused by heart, liver, or kidney disease). The thiazides and thiazide-like diuretics reduce the risk of death, stroke, heart attack and heart failure due to hypertension. ***Furosemide*** is a ***loop diuretic*** (water pill) that prevents your body from absorbing too much salt, allowing the salt to instead be passed in your urine. Furosemide treats fluid retention (edema) in people with congestive heart failure, liver disease, or a kidney disorder such as nephrotic syndrome. This medication is also used to treat high blood pressure (hypertension).	monitoring for early symptoms is sufficient. By monitoring for early symptoms. The proposed PIL contains the following information regarding interactions with ACE-inhibitors and Angiotensin II antagonists, and also diuretics (furosemide, thiazides): ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you are dehydrated, for instance due to sickness, diarrhoea or the use of diuretics (used to treat excess fluid in the body); ***Other medicines and <Invented name>*** Some medicines can affect the way other medicines work. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription: - ACE inhibitors or angiotensin II antagonists (used for high blood pressure and heart failure); - Diuretics (used to treat excess fluid in the body);

	Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. The concurrent use of NSAIDs with thiazide diuretics may exacerbate congestive heart failure and increase the risk of hospitalisation. Diuretics may increase the risk of NSAID-induced acute renal failure.	
Drugs metabolized by CYP2D6 – increased systemic exposure of CYP2D6 substrates and risk of adverse effects **Poor CYP2C9 metabolizers – increased systemic exposure of celecoxib and risk of adverse effects** **Fluconazole – increased risk of celecoxib adverse effects**	Enzymes produced from the cytochrome P450 genes are involved in the formation (synthesis) and breakdown (metabolism) of various molecules and chemicals within cells. Cytochrome P450 enzymes play a role in the synthesis of many molecules including steroid hormones, certain fats (cholesterol and other fatty acids), and acids used to digest fats (bile acids). Additional cytochrome P450 enzymes metabolize external substances, such as medications that are ingested, and internal substances, such as toxins that are formed within cells. There are approximately 60 CYP genes in humans. Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 should be done with caution. Significant interactions may occur when celecoxib is administered together with drugs that inhibit CYP2C9. *In vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding interactions with drugs metabolized by CYP2D6 and poor CYP2C9 metabolisers, and also fluconazole ***Other medicines and <Invented name>*** Some medicines can affect the way other medicines work. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription: - Fluconazole and rifampicin (used to treat fungal and bacterial infections);

	Fluconazole is a triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infections. Concomitant administration of fluconazole can resulted in increase of celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.	

Important potential risks		
	What is known	**Preventability**
Cardiovascular events in patients under the age of 50 years or with short term therapy	Anyone who is at risk for or who has cardiovascular disease (coronary artery disease) may have a further increase in risk of heart attacks when taking an NSAID. This includes people who have experienced a heart attack, angina (chest pain due to narrowed arteries in the heart), a stroke, or narrowed arteries to the brain. As a result, people who have or who are at risk for coronary artery disease are generaly advised to avoid NSAIDs or, if that is not possible, to take the lowest possible dose of NSAID for the shortest possible time.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. No missing information, the proposed PIL advises about cardiovascular events. PIL contains the following information regarding cardiovascular events in patients under the age of 50 years or with short term therapy ***Do not take <Invented name>*** - if you have heart failure, established ischaemic heart disease, or cerebrovascular disease, e.g. you have been diagnosed with a heart attack, stroke, or transient ischaemic attack (temporary reduction of blood flow to the brain; also known as "mini-stroke"), angina, or blockages of blood vessels to the heart or brain; - if you have or have had problems with your blood circulation (peripheral arterial disease) or if you have had surgery on the arteries of your legs;

		Warnings and precautions ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if you smoke, have diabetes, raised blood pressure or raised cholesterol; - if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you; As with other NSAIDs (e.g. ibuprofen or diclofenac) this medicine may lead to an increase in blood pressure, and so your doctor may ask to monitor your blood pressure on a regular basis. ***How to take <Invented name>*** Your doctor will tell you what dose you should take. As the risk of side effects associated with heart problems may increase with dose and duration of use, it is important that you use the lowest dose that controls your pain and you should not take <Invented name> for longer than necessary to control symptoms.
Aplastic anemia	***Anemia*** due to failure of the bone marrow to produce red and white blood cells as well as platelets. Aplastic anemia frequently occurs without a known cause. Known causes include exposure to chemicals (for example, benzene, toluene in glues, insecticides, solvents), drugs (for example, chemotherapy drugs, gold, seizure medications, antibiotics), viruses (for instance, HIV, Epstein-Barr), radiation, immune conditions (for example, systemic lupus erythematosus, rheumatoid arthritis), pregnancy, paroxysmal nocturnal hemoglobinuria, and inherited	Routine pharmacovigilance by monitoring for early symptoms is sufficient. No missing information, the proposed PIL contains the following information regarding aplastic anemia: adverse drug reaction as anemia is listed in PIL. This is a generic application. The proposed PIL complies with the innovator's product. When new information that may impact the current safety specification will be received, additional safety actions in regards to the Pharmacovigilance plan or additional Risk minimization measures will be taken.

	disorders (for example, Fanconi anemia).	
Chest pain/discomfort	***Pain in the chest*** that can be a result of many things, including angina, heart attack (coronary occlusion), and other important diseases. Chest pain is a warning to seek medical attention, so one should try not to ignore chest pain and 'work through it.'	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding chest pain: adverse drug reaction is listed in PIL. This is a generic application. The proposed PIL complies with the innovator's product. When new information that may impact the current safety specification will be received, additional safety actions in regards to the Pharmacovigilance plan or additional Risk minimization measures will be taken.
Interstitial lung disease	***Interstitial lung disease*** is a general category that includes many different lung conditions. All forms of interstitial lung disease cause thickening of the interstitium, a part of the lungs' anatomic structure. The thickening can be due to inflammation, scarring, or extra fluid (edema). Because of the long-term use of some drugs (e.g., NSAIDs) and their harmful effects scarring of lung tissue may occur. The progress of the disease depends on dose of the drug used.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL does not contain the information regarding interstitional lung disease. This is a generic application. The proposed PIL complies with the innovator's product. When new information that may impact the current safety specification will be received, additional safety actions in regards to the Pharmacovigilance plan or additional Risk minimization measures will be taken.
Atrial fibrilation	***Atrial fibrillation*** is an abnormal rhythm of the heart. Symptoms of atrial fibrillation include palpitations, dizziness, fainting, weakness, fatigue, shortness of breath, and chest pain although some people have no symptoms.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. The proposed PIL contains the following information regarding atrial fibrilation: adverse drug reaction as irregular heartbeat is listed in PIL. This is a generic application. The proposed PIL complies with the innovator's product. When new information that may impact the

		current safety specification will be received, additional safety actions in regards to the Pharmacovigilance plan or additional Risk minimization measures will be taken.

Important missing information		
	What is known	**Preventability**
Use in pregnancy and lactation	Patients should be informed that in late pregnancy celecoxib should be avoided because it may cause premature closure of the ductus arteriosus.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. No missing information, the proposed PIL contains the following information about use in pregnancy and breast-feeding: ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** <Invented name> may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems to become pregnant. ***Pregnancy and breast-feeding and fertility*** If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. <Invented name> must not be used by women who are pregnant or can become pregnant (i.e. women of child bearing potential who are not using adequate contraception) during ongoing treatment. If you become pregnant during treatment with <Invented name> you should discontinue the treatment and contact your doctor for alternative treatment. <Invented name> must not be used during breast-feeding.
Use in cirrhotic	***Cirrhosis*** is a condition in which the liver slowly deteriorates and	Routine pharmacovigilance by monitoring for early symptoms is

patients	malfunctions due to chronic injury. Scar tissue replaces healthy liver tissue, partially blocking the flow of blood through the liver. Cirrhosis is not caused by trauma to the liver or other acute, or short-term, causes of damage. Usually years of chronic injury are required to cause cirrhosis. A one new study finds celecoxib may be safe and effective to use on a short-term basis in patients with stable cirrhosis of the liver.	sufficient. No missing information, the proposed PIL contains the following information regarding liver reactions: ***Do not take <Invented name>*** - if you have severe liver disease; ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you; Some cases of severe liver reactions, including severe liver inflammation, liver damage, liver failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Of the cases that reported time to onset, most severe liver reactions occurred within one month of start of treatment. ***How to take <Invented name>*** ***<u>Kidney or liver problems:</u>*** make sure your doctor knows if you have liver or kidney problems as you may need a lower dose.
Use in renal impairment	Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Celecoxib has not been evaluated in patients with severe renal impairment, therefore the use of celecoxib is not recommended in patients with advanced renal disease. If celecoxib therapy must be used in patients with severe renal impairment, close monitoring of renal function is recommended.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. No missing information, the proposed PIL contains the following information regarding use in renal impairment: ***Do not take <Invented name>*** - if you have severe kidney disease; ***Warnings and precautions*** ***Talk to your doctor or pharmacist before taking <Invented name> if any of the following applies to you:*** - if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you;

		How to take <Invented name> ***<u>Kidney or liver problems:</u>*** make sure your doctor knows if you have liver or kidney problems as you may need a lower dose.
Use in children (risk of off-label-use)	Celecoxib is not indicated for use in children.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. No missing information, the proposed PIL contains the following information about use in children: ***How to take <Invented name>*** ***<u>Use in children:</u>*** <Invented name> is for adults only, it is not for use in children. This is a generic application. The proposed PIL complies with the innovator's product. When new information that may impact the current safety specification will be received, additional safety actions in regards to the Pharmacovigilance plan or additional Risk minimization measures will be taken.

VI.2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimisation measures are considered necessary.

VI.2.6 Planned post authorisation development plan (if 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.