PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.1.1. Summary of Safety Concerns

Table 62. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Cardiovascular thrombotic events
	Gastrointestinal ulceration-related events
	Renal toxicity, fluid retention, and edema
	Hypertension
	Hypersensitivity reactions
	Severe skin reactions
	Severe hepatic reactions
Important potential risks	None
Missing information	None

VI.1.2. Summary of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

There are no ongoing or planned studies at this time.

VI.1.3. Summary of Post-Authorisation Efficacy Development Plan

There is no post-authorisation efficacy development plan at this time.

VI.1.4. Summary of Risk Minimisation Measures

A summary of risk minimisation measures is presented in Table 63.

Table 63. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Cardiovascular thrombotic events	EU SmPC Sections: 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.1 Pharmacodynamic properties PL Sections: 2. What you need to know before you take Celebra 3. How to take Celebra 4. Possible side effects	None proposed
Gastrointestinal ulcer-related events	EU SmPC Sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects PL Sections: 2. What you need to know before you take Celebra 4. Possible side effects	None proposed
Renal toxicity, fluid retention, and edema	EU SmPC Sections: 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects 5.2 Pharmacokinetic properties PL Sections: 2. What you need to know before you take Celebra 3. How to take Celebra 4. Possible side effects	None proposed
Hypertension	EU SmPC Sections: 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects PL Sections: 2. What you need to know before you take Celebra 4. Possible side effects	None proposed

Table 63. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Hypersensitivity reactions	EU SmPC Sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects PL Sections: 2. What you need to know before you take Celebra 4. Possible side effects	None proposed
Severe skin reactions	EU SmPC Sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects PL Sections: 2. What you need to know before you take Celebra 4. Possible side effects	None proposed
Severe hepatic reactions	EU SmPC Sections: 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.2 Pharmacokinetic properties PL Sections: 2. What you need to know before you take Celebra 3. How to take Celebra 4. Possible side effects	None proposed

EU=European Union; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

VI.2.1.1. Osteoarthritis

Osteoarthritis (OA) is a common type of joint disease that mostly affects the slippery tissue that covers the ends of a joint (cartilage) and allows bones to glide over each other. When the top layer of cartilage breaks down, bones rub together; this causes pain, swelling, and loss of motion of the joints.[123] OA is a chronic condition that occurs predominantly in older adults (≥65 years of age).[1,2] OA is diagnosed in 2.8 to 18.3% of adults in the EU, depending on the country.[7] OA is one of the leading causes of pain, loss of function, and disability among adults,[9,10] and accounted for nearly 3.2 million years of "healthy" life lost in the European Region in 2012.[13] Compared with the general population, deaths from all causes, deaths involving the heart and blood vessels (cardiovascular), and dementia among adults with OA are 1.6, 1.7, and 2 times higher, respectively.[2]

VI.2.1.2. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic disease that causes pain, stiffness, swelling, and limitation in the motion and function of multiple joints. Other organs such as the heart and blood vessels may also be affected.[124]

According to published reports, the annual occurrence rate of RA varies between 20 and 50 cases per 100,000 in North American and Northern European countries, and it may be lower in Southern European countries.[15] RA is a debilitating illness with numerous complications that reduce quality of life and increase the risk of death.[21] In the European Region, RA accounted for >1 million years of "healthy" life lost in 2012.[13] Death rates are 1.3 to 3 times higher for RA patients than for the general population.[27] The risk of RA increases with age and is higher among women and Native American populations.[20,21,22]

VI.2.1.3. Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis that primarily affects the spine. Shoulders, hips, ribs, heels, and small joints in the hands and feet may also be involved.[125] Onset occurs typically in the mid-20s.[32,33] In Western populations, AS occurs in approximately 1.5 to 7.3 out of every 100,000 persons a year.[27,29,30] The number of people suffering from AS varies geographically, depending on genetic differences in populations.[31,32] AS is associated with substantial reductions in quality of life due to chronic pain, other chronic medical conditions, diminished bending ability, and the resulting difficulty in completing routine tasks or work activities.[42] The death rate of AS patients is 1.3 to 1.8 times higher than that of the general population.[40]

VI.2.2. Summary of Treatment Benefits

Several clinical studies have been performed to confirm the effectiveness and safety of celecoxib in a type of joint disease that results from breakdown of joint cartilage and underlying bone (osteoarthritis), a disease causing inflammation of the joints (rheumatoid arthritis), and a disease causing inflammation of the joints of the spine (ankylosing spondylitis).

- Osteoarthritis – Celecoxib was compared with placebo (a dummy treatment) for the treatment of inflammation and pain of the knee and hip in approximately 4200 patients, in studies lasting up to 12 weeks.

- Rheumatoid arthritis – Celecoxib was compared with placebo for the treatment of inflammation and pain in approximately 2100 patients, in studies lasting up to 24 weeks.

- Ankylosing spondylitis – Celecoxib was compared with placebo for the treatment of the signs and symptoms of AS in 896 patients, in studies lasting up to 12 weeks.

Celecoxib at doses of 100 mg twice daily, 200 mg once daily, 200 mg twice daily, and 400 mg once daily in these studies demonstrated significant reduction in joint tenderness/pain/swelling and improvement in the overall state of the disease (global disease activity) and function compared to placebo.

Celecoxib is approved in the EU for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in adults. In some countries outside of the EU, celecoxib is approved for the management of the signs and symptoms of a type of arthritis that causes joint inflammation and stiffness for more than 6 weeks in a child aged 16 or younger (juvenile idiopathic arthritis); management of urgent (acute) pain; and treatment of painful menstrual periods (primary dysmenorrhea).

The decision to prescribe a medicine that belongs to a group of medicines called nonsteroidal anti-inflammatory drugs (specifically a sub-group known as COX-2 inhibitors) should be based on the individual patient's overall risks.

VI.2.3. Unknowns Relating to Treatment Benefits

The clinical studies were designed to enroll subjects as close to the possible target population; however, in the clinical practice setting, there will be patients who are on concurrent medications or who have other chronic medical conditions (comorbidities) that have not been studied with celecoxib use and that may affect the medical outcome.

VI.2.4. Summary of Safety Concerns

Table 64. Important Identified Risks

Risk	What is Known	Preventability
Blood clots to the heart or brain (Cardiovascular thrombotic events)	The risks for events involving the heart and blood vessels may increase with celecoxib dose and duration of exposure. Up to 1 in 10 people treated with celecoxib may experience heart attack, and up to 1 in 100 people may experience stroke. Bleeding within the brain causing death may affect up to 1 in 10,000 people. Blood clot in the blood vessels in the lungs (pulmonary embolism) has been rarely reported in arthritis patients who took celecoxib. In clinical studies not associated with arthritis or other arthritic conditions, where celecoxib was taken at doses of 400 mg per day for up to 3 years, blood clot usually in the leg, which may cause pain, swelling, or redness of the calf (deep vein thrombosis) has been observed in at least 1 in 100 people.	Patients with significant risk factors for events involving the heart and blood vessels (e.g., high blood pressure, high levels of fat in the blood, diabetes mellitus, and/or smoking) should only be treated with celecoxib after careful consideration. The shortest duration possible and the lowest effective daily dose should be used. Celecoxib should not be used if a patient has any of these conditions: • heart failure, established ischaemic heart disease, or cerebrovascular disease, e.g., diagnosed with a heart attack, stroke, or temporary reduction of blood flow to the brain (transient ischaemic attack or "mini-stroke"), angina, or blockages of blood vessels to the heart or brain; • problems with blood circulation (peripheral arterial disease) or had surgery on the arteries of the legs.

Table 64. Important Identified Risks

Risk	What is Known	Preventability
Ulcer or bleeding in stomach or intestines (Gastrointestinal ulceration-related events)	Bleeding (ulcers) in the stomach, gullet (oesophagus), or intestines; rupture of the intestine (can cause stomach ache, fever, nausea, vomiting, intestinal blockage), dark or black stools, or inflammation of the gullet may affect up to 1 in 1000 people treated with celecoxib.	Celecoxib should not be used if a patient has **current** ulcer or bleeding in the stomach or intestines. Celecoxib should be used with caution in patients with **previous** ulcer or bleeding in the stomach and intestines.
Kidney disease, fluid buildup in the body causing swelling (Renal toxicity, fluid retention, and oedema)	Clinical trials with celecoxib have shown kidney effects similar to those observed with NSAIDs. Patients at greatest risk for kidney disease are those with impaired kidney function, heart failure, liver dysfunction, those taking medicines used to treat excess body fluid (diuretics), medicines used for high blood pressure and heart failure (ACE-inhibitors, angiotensin II receptor antagonists), and the elderly. Fluid or water retention (oedema) has been observed in patients taking celecoxib. Up to 1 in 1000 people treated with celecoxib may experience acute kidney failure. Up to 1 in 10,000 people treated with celecoxib may experience inflammation of the kidneys and other kidney problems (such as nephrotic syndrome and minimal change disease, which may be accompanied by symptoms such as water retention, foamy urine, fatigue, and a loss of appetite).	Experience with celecoxib in patients with mild or moderate renal impairment is limited; therefore, such patients should be treated with caution. Careful monitoring is required for patients at increased risk. Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with celecoxib. Celecoxib should be used with caution in patients with history of heart problems that can cause shortness of breath or ankle swelling (cardiac failure), left ventricle dysfunction, or high blood pressure (hypertension), and in patients with existing fluid retention (oedema) from any other reason.
High blood pressure (Hypertension)	As with other NSAIDs (e.g., ibuprofen or diclofenac), celecoxib may lead to an increase in blood pressure or worsening of existing high blood pressure. High blood pressure, including worsening of existing high blood pressure, may affect more than 1 in 10 people treated with celecoxib.	Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy. Celecoxib should be used with more caution in patients taking medicines to treat high blood pressure and heart failure or those used to treat excess bloody fluid (ACEIs, ARBs, diuretics, and beta-blockers).
Serious allergic reactions (Hypersensitivity reactions)	Serious allergic reactions (including potentially fatal anaphylactic shock) may affect up to 1 in 10,000 people treated with celecoxib.	Celecoxib should not be used in patients who have hypersensitivity or allergic-type reactions after taking acetylsalicylic acid (aspirin) or other NSAIDs including COX-2

Table 64. Important Identified Risks

Risk	What is Known	Preventability
		inhibitors. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Serious skin conditions (Severe skin reactions)	Serious skin conditions, such as Stevens-Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis (can cause rash, blistering or peeling of the skin) and acute generalised exanthematous pustulosis (symptoms include the skin becoming red with swollen areas covered in numerous small pustules), have been reported in up to 1 in 10,000 people treated with celecoxib.	Celecoxib should not be used in patients who have hypersensitivity or allergic-type reactions after taking acetylsalicylic acid (aspirin) or other NSAIDs including COX-2 inhibitors. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Serious liver problems (Severe hepatic reactions)	Up to 1 in 1000 people may experience severe liver inflammation (hepatitis) in association with celecoxib use. Liver failure, liver damage, and severe liver inflammation (fulminant hepatitis), sometimes fatal or requiring liver transplant, may affect up to 1 in 10,000 people treated with celecoxib. Of the cases that reported time to onset, most severe liver reactions occurred within one month of start of treatment.	Celecoxib should not be used in patients with serious liver impairment. Celecoxib should be used with caution when treating patients with moderate liver impairment (Child-Pugh Class B), and initiated at half the recommended dose. Careful monitoring should be given to patients with signs of liver problems, and discontinuation of celecoxib should be considered when deterioration of liver function is suspected.

VI.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics that 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

There are no planned post-authorisation studies.

Studies that are a Condition of the Marketing Authorisation

None.

VI.2.7. Summary of Changes to the Risk Management Plan Over Time

Major changes to the Risk Management Plan over time are shown in Table 65.

Table 65. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	28 February 2005	**Safety risks:** • Cardiovascular thromboembolic events • Cardiorenal events	Initial Risk Management Plan
2.0	03 May 2011	**Important identified risks:** • Cardiovascular thrombotic events • Gastrointestinal ulceration-related events • Renal toxicity, fluid retention, and edema • Hypertension • Hypersensitivity reactions • Severe skin reactions • Severe hepatic reactions • Safety profile in juvenile idiopathic arthritis (JIA) **Important potential risks:** None **Important missing information:** None	Updated to align with the European Medicines Agency (EMA) RMP template.
3.0	22 February 2012	**Important identified risks:** • Cardiovascular thrombotic events • Gastrointestinal ulceration-related events • Renal toxicity, fluid retention, and edema • Hypertension • Hypersensitivity reactions • Severe skin reactions • Severe hepatic reactions **Important potential risks:** None **Important missing information:** Safety profile in juvenile idiopathic arthritis	Updated in association with Periodic Safety Update Report (PSUR) 14. Reason for re-classification of safety profile in JIA (from Important identified risk to Important missing information): - The safety and efficacy of celecoxib in children have not been studied beyond 6 months duration or in patients with body weight less than 10 kg (22 lbs), or in patients with active systemic JIA features.

Table 65. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
4.0	05 October 2017	**Important identified risks:** • Cardiovascular thrombotic events • Gastrointestinal ulceration-related events • Renal toxicity, fluid retention, and edema • Hypertension • Hypersensitivity reactions • Severe skin reactions • Severe hepatic reactions **Important potential risks:** None **Missing information:** None	Updated to include data from the completed PRECISION study (A3191172). 'Safety profile in JIA' was removed as missing information, for the following reasons: - JIA is not an approved indication in the EU; - JIA patients are not the targeted population for this EU-RMP. Drug interactions with CYP2C9 inducers, Acetylsalicylic acid, and CYP2D6 substrates (Dextromethorphan and Metoprolol) were added as important identified interactions. Converted from modular format to integrated format to align with the EMA Guideline on Good Pharmacovigilance Practices Module V – Risk management systems (Revision 1, April 2014).