ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES AND NORWAY AND ICELAND

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Austria	Pharmacia Austria Ges.m.b.H., Oberlaaerstraße 247-251 A-1100 Wien AUSTRIA	Celebrex 100 mg Hartkapseln	100 mg	Capsule, hard	Oral use
Austria	Pharmacia Austria Ges.m.b.H., Oberlaaerstraße 247-251 A-1100 Wien AUSTRIA	Celebrex 200 mg Hartkapseln	200 mg	Capsule, hard	Oral use
Austria	Pharmacia Austria Ges.m.b.H., Oberlaaerstraße 247-251 A-1100 Wien AUSTRIA	Solexa 100 mg Hartkapseln	100 mg	Capsule, hard	Oral use
Austria	Pharmacia Austria Ges.m.b.H., Oberlaaerstraße 247-251 A-1100 Wien AUSTRIA	Solexa 200 mg Hartkapseln	200 mg	Capsule, hard	Oral use
Belgium	Pharmacia Twin Squares Culliganllaan, 1 c B-1831 DIEGEM Belgium	Celebrex	100 mg	Capsule, hard	Oral use
Belgium	Pharmacia Twin Squares Culliganllaan, 1 c B-1831 DIEGEM Belgium	Celebrex	200 mg	Capsule, hard	Oral use
Belgium	Pharmacia S.A. Rijksweg 12	Solexa	100 mg	Capsule, hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	B-2870 Puurs Belgium				
Belgium	Pharmacia S.A. Rijksweg 12 B-2870 Puurs Belgium	Solexa	200 mg	Capsule, hard	Oral use
Denmark	Pfizer Aps Lautrupvang 8 DK-2750 Ballerup Denmark	Celebra	100 mg	Capsule, hard	Oral use
Denmark	Pfizer Aps Lautrupvang 8 DK-2750 Ballerup Denmark	Celebra	200 mg	Capsule, hard	Oral use
Denmark	Pfizer Aps Lautrupvang 8 DK-2750 Ballerup Denmark	Solexa	100 mg	Capsule, hard	Oral use
Denmark	Pfizer Aps Lautrupvang 8 DK-2750 Ballerup Denmark	Solexa	200 mg	Capsule, hard	Oral use
Finland	Pharmacia Oy P.O Box 45 02601 ESPOO FINLAND	Celebra	100 mg	Capsule Hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Finland	Pharmacia Oy P.O Box 45 02601 ESPOO FINLAND	Celebra	200 mg	Capsule Hard	Oral use
Finland	Pharmacia Oy P.O Box 45 02601 ESPOO FINLAND	Solexa	100 mg	Capsule Hard	Oral use
Finland	Pharmacia Oy P.O Box 45 02601 ESPOO FINLAND	Solexa	200 mg	Capsule Hard	Oral use
France	PHARMACIA SAS 1 rue Antoine Lavoisier F-78280 GUYANCOURT FRANCE	Celebrex	100 mg	Capsule	Oral use
France	PHARMACIA SAS 1 rue Antoine Lavoisier F-78280 GUYANCOURT France	Celebrex	200 mg	Capsule	Oral use
France	CARDEL 1 rue Antoine Lavoisier F-78280 GUYANCOURT France	Solexa	100 mg	Capsule	Oral use
France	CARDEL	Solexa	200 mg	Capsule	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	1 rue Antoine Lavoisier F-78280 GUYANCOURT France				
Germany	Pharmacia GmbH Am Wolfsmantel 46 D-91059 Erlangen GERMANY	Celebra 100 mg Hartkapseln	100	Capsule Hard	Oral use
Germany	Pharmacia GmbH Am Wolfsmantel 46 D-91059 Erlangen GERMANY	Celebra 200 mg Hartkapseln	200	Capsule Hard	Oral use
Germany	Pharmacia GmbH Am Wolfsmantel 46 D-91059 Erlangen GERMANY	Celebrex 100 mg Hartkapseln	100	Capsule Hard	Oral use
Germany	Pharmacia GmbH Am Wolfsmantel 46 D-91059 Erlangen GERMANY	Celebrex 200 mg Hartkapseln	200	Capsule Hard	Oral use
Greece	Pfizer Hellas AE 5 Alketou St 116 33 Athens GREECE	Aclarex	100 mg	Capsule hard	Oral use
Greece	Pfizer Hellas AE 5 Alketou St 116 33 Athens	Aclarex	200 mg	Capsule hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	GREECE				
Greece	Pharmacia hellas 2 Kalavriton 145 62 Nea kifisia Athens GREECE	Celebrex	100 mg	Capsule hard	Oral use
Greece	Pharmacia hellas 2 Kalavriton 145 62 Nea kifisia Athens GREECE	Celebrex	200 mg	Capsule hard	Oral use
Ireland	Monsanto Plc PO Box 53 Lane End Road High Wycombe Buckinghamshire HP12 4 HL UNITED KINGDOM	Celebrex	100 mg	Capsule hard	Oral use
Ireland	Monsanto Plc PO Box 53 Lane End Road High Wycombe Buckinghamshire HP12 4 HL UNITED KINGDOM	Celebrex	200 mg	Capsule hard	Oral use
Ireland	Monsanto Plc PO Box 53	Solexa	100 mg	Capsule hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Lane End Road, High Wycombe Buckinghamshire HP12 4 HL UNITED KINGDOM				
Ireland	Monsanto Plc PO Box 53 Lane End Road High Wycombe Buckinghamshire HP12 4 HL UNITED KINGDOM	Solexa	200 mg	Capsule hard	Oral use
Italy	Pharmacia Italia S.p.A. Via Robert Kock, 1-2 I-20152 Milano ITALY	Artilog	100 mg	Capsule, hard	Oral use
Italy	Pharmacia Italia S.p.A. Via Robert Kock, 1-2 I-20152 Milano ITALY	Artilog	200 mg	Capsule, hard	Oral use
Italy	Sefarma S.r.l. Via Robert Kock, 1-2 I-20152 Milano ITALY	Artrid	200 mg	Capsule, hard	Oral use
Italy	Sefarma S.r.l. Via Robert Kock, 1-2 I-20152 Milano	Artrid	100 mg	Capsule, hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	ITALY				
Italy	Pharmacia Italia S.p.A. Via Robert Kock, 1-2 I-20152 Milano ITALY	Celebrex	100 mg	Capsule, hard	Oral use
Italy	Pharmacia Italia S.p.A. Via Robert Kock, 1-2 I-20152 Milano ITALY	Celebrex	200 mg	Capsule, hard	Oral use
Italy	Pfizer Italiana S.p.A. Via Valbondione, 113 I-00188 Roma ITALY	Solexa	100 mg	Capsule, hard	Oral use
Italy	Pfizer Italiana S.p.A. Via Valbondione, 113 I-00188 Roma ITALY	Solexa	200 mg	Capsule, hard	Oral use
Luxembourg	Pharmacia S.A. Rijksweg 12 B-2870 Puurs BELGIUM	Celebrex	100 mg	Capsule	Oral use
Luxembourg	Pharmacia S.A. Rijksweg 12 B-2870 Puurs BELGIUM	Celebrex	200 mg	Capsule	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Pharmacia S.A. Rijksweg 12 B-2870 Puurs BELGIUM	Solexa	100 mg	Capsule	Oral use
Luxembourg	Pharmacia S.A. Rijksweg 12 B-2870 Puurs BELGIUM	Solexa	200 mg	Capsule	Oral use
The Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel The Netherlands	Celebrex 100 mg	100 mg	Capsule	Oral use
The Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel The Netherlands	Celebrex 200 mg	200 mg	Capsule	Oral use
The Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel The Netherlands	Solexa	100 mg	Capsule	Oral use
The Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel The Netherlands	Solexa	200 mg	Capsule	Oral use
Norway	Pharmacia Norge AS Lilleakerveien. 2 B	Celebra	100 mg	Capsule, hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	N-0283 Oslo NORWAY				
Norway	Pharmacia Norge AS Lilleakerveien. 2 B N-0283 Oslo NORWAY	Celebra	200 mg	Capsule, hard	Oral use
Portugal	Laboratórios Pfizer, Lda. Estrada Nacional 10, Km 16,Porto Zemouto 2830-411 Coina Portugal	Celebrex 100 mg	100 mg	Capsule, hard	Oral use
Portugal	Laboratórios Pfizer, Lda. Estrada Nacional 10, Km 16,Porto Zemouto 2830-411 Coina Portugal	Celebrex 200 mg	200 mg	Capsule, hard	Oral use
Portugal	Laboratório Medinfar - Produtos Farmacêuticos, S.A. Rua Manuel Ribeiro de Pavia, 1 1º - Venda Nova 2700-547 Amadora PORTUGAL	Solexa 100 mg	100 mg	Capsule, hard	Oral use
Portugal	Laboratório Medinfar - Produtos Farmacêuticos, S.A. Rua Manuel Ribeiro de Pavia, 1 1º - Venda Nova 2700-547 Amadora	Solexa 200 mg	200 mg	Capsule, hard	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	PORTUGAL				
Spain	Pharmacia Spain S.A. Avda. de Europa 20-B Parque Empresarial La Moraleja E-28108 Alcobendas, Madrid SPAIN	Artilog 100 mg	100 mg	Capsule	Oral use
Spain	Pharmacia Spain S.A. Avda. de Europa 20-B Parque Empresarial La Moraleja E-28108 Alcobendas, Madrid SPAIN	Artilog 200 mg	200 mg	Capsule	Oral use
Spain	Pharmacia Spain S.A. Avda. de Europa 20-B Parque Empresarial La Moraleja E-28108 Alcobendas, Madrid SPAIN	Celebrex 100 mg	100 mg	Capsule	Oral use
Spain	Pharmacia Spain S.A. Avda. de Europa 20-B Parque Empresarial La Moraleja E-28108 Alcobendas, Madrid SPAIN	Celebrex 200 mg	200 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Aclarix	100 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm	Aclarix	200 mg	Capsule	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	SWEDEN				
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Celebra	100 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Celebra	200 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Celora	100 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Celora	200 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Solexa	100 mg	Capsule	Oral use
Sweden	Pharmacia Sverige AB S-112 87 Stockholm SWEDEN	Solexa	200 mg	Capsule	Oral use
United Kingdom	Pharmacia Ltd Davy Avenue Milton Keynes Buckinghamshire MK5 8PH UK	Celebrex	100 mg	Capsule	Oral use

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Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Pharmacia Ltd Davy Avenue Milton Keynes Buckinghamshire MK5 8PH UK	Celebrex	200 mg	Capsule	Oral use
United Kingdom	Pharmacia Ltd Davy Avenue Milton Keynes Buckinghamshire MK5 8PH UK	Solexa	100 mg	Capsule	Oral use
United Kingdom	Pharmacia Ltd Davy Avenue Milton Keynes Buckinghamshire MK5 8PH UK	Solexa	200 mg	Capsule	Oral use

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ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

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SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING CELECOXIB, ETORICOXIB, PARECOXIB, ROFECOXIB AND VALDECOXIB

- INTRODUCTION

The COX-2 inhibitors celecoxib, etoricoxib, rofecoxib, parecoxib and valdecoxib, comprise a relatively new group of substances whose common pharmacological action is the selective inhibition of cyclooxygenase-2. COX-2 inhibitors have been introduced in medical practice for treatment of patients with chronic inflammatory degenerative diseases such as rheumatoid arthritis and osteoarthritis.
Rofecoxib and celecoxib have been first authorised in the EU for these indications, and subsequently rofecoxib for treatment of acute pain and pain due to primary dysmenorrhoea. Etoricoxib received later authorisation for rheumatic diseases, including gouty athritis, in some EU-member states. Valdecoxib is authorised for the rheumatic indications and primary dysmenorrhoea and was authorised after start of the referral procedure. Parecoxib, a prodrug of valdecoxib, is authorised for short-term treatment of post-surgical pain, when used intravenously or intramuscularly. Celecoxib received an authorisation in October 2003 in an orphan drug indication (familial adenomatous polyposis).

COX-2 inhibitors have been investigated in large clinical studies, and a large body of data - toxicological, pharmacological, clinical, and epidemiological - is available today. When first authorised there were insufficient data showing a benefit in long-term treatment of rheumatoid arthritis and osteoarthritis patients compared to usual NSAIDs. Moreover, knowledge of tolerability under normal use of COX-2 inhibitors, ie. outside clinical studies, was limited as with nearly all new chemical entities introduced in broad medical practice. Large clinical trials (VIGOR: rofecoxib versus naproxen, CLASS: celecoxib versus diclofenac or ibuprofen) using high doses have been conducted and published in this respect, especially looking at gastrointestinal (GI) tolerability.

In July 2002, France requested the CPMP to give its opinion under Article 31 of Directive 2001/83 EC as amended, on whether the marketing authorisations for medicinal products containing COX-2 inhibitors (celecoxib, etoricoxib, rofecoxib, valdecoxib and parecoxib) should be maintained, changed, suspended or withdrawn by reassessing the benefit-risk profile of the class of products.

The CPMP, during its meeting held from 23 to 25 July 2002 decided to start a referral procedure under Article 31 of Directive 2001/83/EC as amended, for medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib. The questions identified related to gastrointestinal and cardiovascular safety. In October 2002, the CPMP asked additional questions relating to serious hypersensitivity reactions (anaphylaxis and angioedema) and serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis in patients treated with COX-2 inhibitors.

- EFFICACY ISSUES

Efficacy has been demonstrated for celecoxib in the treatment of rheumatoid arthritis or osteoarthritis. Efficacy was superior to placebo and similar to non-selective NSAIDs (diclofenac, naproxen, ibuprofen) in comparative clinical settings, equipotent dosage, and duration of treatment.

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- **SAFETY ISSUES**

Gastrointestinal toxicity

Available data indicated that significant and consistent gastrointestinal benefit of COX-2 inhibitors compared with conventional NSAIDs has not been demonstrated. The clinical data provided specifically for celecoxib were consistent with a GI benefit compared with naproxen. GI safety concerning complicated ulcers was similar to ibuprofen and diclofenac.
The CPMP decided to add a general statement in section 4.4 "Special warnings and special precautions for use" and 5.1 "Pharmacodynamic properties" of the SPC for all COX-2 inhibitors relating to patients at risk of developing gastrointestinal complications with NSAIDs.

It is unknown whether the gastrointestinal toxicity profile of COX-2 inhibitors in association with acetylsalicylic acid is inferior to conventional NSAIDs given with acetylsalicylic acid but there is no evidence to suggest it would be superior. Based on the current data on celecoxib require that the product information should be updated to include the potential for increase in gastrointestinal toxicity compared with COX-2 inhibitors or acetylsalicylic acid alone.
Further to discussions and considering the assessment of the data presented for the others COX-2 inhibitors, the CPMP decided to update section 4.4 "Special warnings and special precautions for use" of the Summary of Products Characteristics (SPC) regarding concomitant use of all COX-2 inhibitors with a general statement on COX-2 inhibitors and acetylsalicylic acid association.

Cardiovascular toxicity

The available pre-clinical data raised concern about cardiovascular (CV) safety, in particular myocardial infarction (MI), however, conflicting results have often been obtained. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions.
It can be considered that there is a trend towards a higher MI risk associated with the use of celecoxib compared to naproxen and diclofenac. In contrast to COX-1 inhibiting NSAIDs, COX-2 inhibitors, including celecoxib, have no anti-platelet effects in therapeutic doses. With respect to CV risk, it can be considered that there may be a small safety disadvantage of COX-2 inhibitors compared to conventional NSAIDs. Therefore, the SPC should be updated for all COX-2 inhibitors, including celecoxib, in its section 4.4 "Special warnings and special precautions for use" by adding a warning statement for patients with a medical history of cardiovascular disease or those using low dose of ASA-treatment for prophylaxis of cardiovascular thrombo-embolic diseases.

Hypersensitivity and serious skin reactions

When celecoxib was compared to NSAIDs, especially to diclofenac, the incidence of skin reactions, especially of rash, was significantly higher in MAA Trial, CLASS and SUCCESS. Results from clinical trials give reason for the conclusion that celecoxib-treated patients are at higher risk for developing rash than diclofenac-treated patients and possibly also at higher risk of developing urticaria than patients treated with other NSAIDs.
Spontaneous reports of hypersensitivity reactions (anaphylaxis/angioedema) were not very frequent for celecoxib. Because of the lack of relevant information no further statement on possible risk factors for the development of angioedema/anaphylaxis in celecoxib-treated patients can be met.

Furthermore, single cases of serious cutaneous adverse reactions, i.e., Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported for celecoxib. The absolute numbers and estimates for frequency suggest that these adverse reactions occur very rarely and frequency seems not to be different from conventional NSAIDs.

In order to assure the attention to this potentially life threatening adverse reactions in clinical practice, the CPMP decided that a general statement relating to hypersensitivity and serious skin reactions will

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be included/modified in section 4.4 “Special warnings and special precautions for use” of all COX-2 inhibitor SPCs.

HARMONISED WORDING FOR ALL COX-2 INHIBITORS SUMMARIES OF PRODUCT CHARACTERISTICS

Further to the assessment of data provided for celecoxib, etoricoxib, rofecoxib, valdecoxib and parecoxib, the CPMP has adopted a harmonised wording, which should be included in the SPC of all COX-2 inhibitors involved in this referral or concerned by the scientific assessment. The wording for celecoxib is the following:

Section 4.4 “Special warnings and special precautions for use”

Because of the possibility for increased adverse reactions at higher doses of celecoxib, other COX-2 inhibitors and NSAIDs, patients treated with celecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see 4.2).

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs), some of them resulting in fatal outcome, have occurred in patients treated with celecoxib.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly,patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is an increased risk of gastrointestinal adverse effects for celecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelets function. Because celecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery) (see 4.5 and 5.1.).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of celecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs including celecoxib during postmarketing surveillance (see 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving celecoxib (see 4.8). Patients with a history of sulphonamide allergy may be at greater risk of hypersensitivity reactions (see 4.3). Celecoxib should be discontinued at the first sign of hypersensitivity.

Section 5.1 “Pharmacodynamic properties”

Celecoxib is an oral,selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily).

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of

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prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas

- The Committee considered the referral made under Article 31 of Directive 2001/83/EC, as amended, for medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib;
- The Committee considered that no new contra-indications should be added in any of the concerned Summaries of Products Characteristics;
- The Committee concluded that a warning should be added concerning the gastrointestinal safety of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib, mainly concerning the association with acetylsalicylic acid;
- The Committee concluded that a warning should be added concerning the cardiovascular safety of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib, mainly concerning the risk of myocardial infarction;
- The Committee concluded that a warning should be added/modified concerning observed or potential serious skin effects and hypersensitivity reactions of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib;
- The Committee, as a consequence considered that the benefit/risk balance of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib remains favourable.

As a consequence, the CPMP recommended the maintenance of the Applications/Marketing Authorisations for medicinal products containing celecoxib referred in Annex I in the symptomatic relief of osteoarthritis (OA) and rheumatoid arthritis (RA) as amended in accordance with the revised SPC as set out in Annex III.

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ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

NOTE:
THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION DECISION CONCERNING THIS REFERRAL FOR ARBITRATION; THE TEXT WAS VALID AT THAT TIME.

AFTER THE CD, THE MEMBER STATE COMPETENT AUTHORITIES WILL UPDATE THE PRODUCT INFORMATION AS REQUIRED. THEREFORE, THIS SPC MAY NOT NECESSARILY REPRESENT THE CURRENT TEXT.

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1. NAME OF THE MEDICINAL PRODUCT

{INVENTED NAME, see Annex I} 100 mg capsule, hard.
{INVENTED NAME, see Annex I } 100 mg capsule.
{INVENTED NAME, see Annex I } 200 mg capsule, hard.
{INVENTED NAME, see Annex I } 200 mg capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg or 200 mg celecoxib.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard or capsule.
Opaque, white with two blue bands marked 7767 and 100.
Opaque, white with two gold bands marked 7767 and 200.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis.

4.2 Posology and method of administration

Osteoarthritis: The usual recommended daily dose is 200 mg taken once daily or in two divided doses. In some patients, with insufficient relief from symptoms, an increased doseof 200 mg twice daily may increase efficacy.

Rheumatoid arthritis: The recommended daily dose is 200-400 mg taken in two divided doses.

The maximum recommended daily dose is 400mg for both indications.

{Invented Name} may be taken with or without food.

Elderly: In the elderly (>65 years), in particular those of less than 50 kg body weight, the lower dose (200 mg per day) should be used initially. The dose may, if needed, later be increased to 400 mg per day (See 4.4 and 5.2).

Hepatic impairment: Treatment should be initiated at half the recommended dose in patients with established moderate liver impairment with a serum albumin of 25-35 g/l. Experience in such patients is limited to cirrhotic patients (See 4.3, 4.4 and 5.2).

Renal impairment: Experience with celecoxib in patients with mild or moderate renal impairment is limited, therefore such patients should be treated with caution. (See 4.3, 4.4 and 5.2).

Children: Celecoxib is not indicated for use in children.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients (see 6.1).

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Known hypersensitivity to sulphonamides
Active peptic ulceration or gastrointestinal (GI) bleeding.
Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

In pregnancy and in women of childbearing potential unless using an effective method of contraception (See 4.5). Celecoxib has been shown to cause malformations in the two animal species studied (See 4.6 and 5.3). The potential for human risk in pregnancy is unknown, but cannot be excluded.

Breast feeding (See 4.6 and 5.3).
Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).

Patients with estimated renal creatinine clearance <30 ml/min.

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

Because of the possibility for increased adverse reactions at higher doses of celecoxib, other COX-2 inhibitors and NSAIDs, patients treated with celecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see 4.2).

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs), some of them resulting in fatal outcome, have occurred in patients treated with celecoxib.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly,patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is an increased risk of gastrointestinal adverse effects for celecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelets function. Because celecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery) (see 4.5 and 5.1.).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of celecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients

As with other drugs known to inhibit prostaglandin synthesis fluid retention and oedema have been observed in patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.

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Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly in whom the lowest effective dose should be used and therefore medically appropriate supervision should be maintained. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs.

Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction may be necessary for individually dose-titrated drugs that are metabolised by CYP2D6 (See 4.5). Patients known to be CYP2C9 poor metabolisers should be treated with caution (see 5.2.).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs including celecoxib during postmarketing surveillance (see 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving celecoxib (see 4.8). Patients with a history of sulphonamide allergy may be at greater risk of hypersensitivity reactions (see 4.3). Celecoxib should be discontinued at the first sign of hypersensitivity.

Celecoxib may mask fever and other signs of inflammation.

In patients on concurrent therapy with warfarin, serious bleeding events have occurred. Caution should be exercised when combining celecoxib with warfarin and other oral anticoagulants (See 4.5).

{Invented Name}100 mg and 200 mg capsules contain lactose (149.7 mg and 49.8 mg, respectively). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with celecoxib is initiated or the dose of celecoxib is changed. (see 4.4). Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly, in patients receiving celecoxib concurrently with warfarin, some of them fatal.

NSAIDs may reduce the effect of diuretics and antihypertensive drugs. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors are combined with celecoxib.

Coadministration of NSAIDs and cyclosporin or tacrolimus have been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when celecoxib and any of these drugs are combined.

Celecoxib can be used with low dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid.(see 5.1)

Pharmacokinetic interactions

Effects of celecoxib on other drugs
Celecoxib is an inhibitor of CYP2D6. During celecoxib treatment, the plasma concentrations of the CYP2D6 substrate dextromethorphan were increased by 136%. The plasma concentrations of drugs that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of drugs which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic drugs, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be

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reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.

In vitro studies have shown some potential for celecoxib to inhibit CYP2C19 catalysed metabolism. The clinical significance of this *in vitro* finding is unknown. Examples of drugs which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethistherone /35 microg ethinylestradiol).

Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically relevant extent.

In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two drugs.

In healthy subjects, co-administration of celecoxib 200mg twice daily with 450mg twice daily of lithium resulted in a mean increase in Cmax of 16% and in AUC of 18% of lithium. Therefore, patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Effects of other drugs on celecoxib

Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200mg single dose of celecoxib and 200mg once daily of fluconazole, a potent CYP2C9 inhibitor, resulted in a mean increase in celecoxib Cmax of 60% and in AUC of 130%. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available for celecoxib. Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see 4.3 and 5.3). The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Celecoxib is contraindicated in pregnancy and in women who can become pregnant (see 4.3 and 4.4). If a woman becomes pregnant during treatment, celecoxib should be discontinued.

There are no studies on the excretion of celecoxib in human milk. Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Women who take celecoxib should not breastfeed.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking celecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

Approximately 7400 patients were treated with celecoxib in controlled trials and of those approximately 2300 have received it for 1 year or longer. The following events have been reported in patients receiving celecoxib in 12 placebo and/or active controlled trials**.** Side-effects listed have a rate

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equal or greater than placebo, and the discontinuation rate due to side effects was 7.1% in patients receiving celecoxib and 6.1% in patients receiving placebo.

Additional events including very rare and isolated reports from post-marketing experience in >5.3 million treated patients are included.

[Very Common (>1/10), Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

Infections and infestations
Common: sinusitis, upper respiratory tract infection
Uncommon: urinary tract infection

Blood and the lymphatic system disorders
Uncommon: anaemia.
Rare: leucopenia, thrombocytopenia

Metabolism and nutrition disorders
Uncommon: hyperkalaemia

Psychiatric disorders
Common: insomnia
Uncommon: anxiety, depression, tiredness.

Nervous system disorders
Common: dizziness
Uncommon: blurred vision, hypertonia, paraesthesia
Rare: ataxia, taste alteration

Ear and labyrinth disorders
Uncommon: tinnitus

Cardiac disorders
Uncommon: palpitations

Vascular disorders
Uncommon: hypertension

Respiratory, thoracic and mediastinal disorders
Common: pharyngitis, rhinitis
Uncommon: cough, dyspnoea

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, dyspepsia, flatulence
Uncommon: constipation, eructation, gastritis, stomatitis, vomiting.
Rare: duodenal**,** gastric and oesophageal ulceration, dysphagia, intestinal perforation, oesophagitis, melaena.

Hepato-biliary disorders
Uncommon: abnormal hepatic function

Skin and subcutaneous tissue disorders
Common: rash.
Uncommon: urticaria.
Rare: alopecia, photosensitivity

Musculoskeletal and connective tissue disorders

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Uncommon: leg cramps

General disorders and administration site conditions
Common: peripheral oedema/ fluid retention.

Investigations
Uncommon: increased SGOT and SGPT, increased creatinine, BUN increased

Reports from postmarketing experience include headache, nausea and arthralgia, also the following very rare (<1/10,000, including isolated cases):

Blood and lymphatic system disorders: pancytopenia.
Immune system disorders: serious allergic reactions, anaphylactic shock.
Psychiatric disorders: confusion, hallucinations.
Nervous system disorders: aggravated epilepsy
Ear and labyrinth disorders: decreased hearing.
Cardiac disorders: congestive heart failure, heart failure, myocardial infarction
Vascular disorders: vasculitis, Respiratory, thoracic and mediastinal disorders : bronchospasm
Gastrointestinal disorders: gastrointestinal haemorrhage, acute pancreatitis.
Hepatobiliary disorders: hepatitis, jaundice.
Skin and subcutaneous tissue disorders: angioedema, isolated reports of skin exfoliation including: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme.
Musculoskeletal and connective tissue disorders: myositis
Renal and urinary disorders: acute renal failure, interstitial nephritis.

4.9 Overdose

There is no clinical experience of overdose. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects for nine days without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided e.g. by eliminating the gastric contents, clinical supervision and, if necessary, the institution of symptomatic treatment. Dialysis is unlikely to be an efficient method of drug removal due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: MO1AH01.

Celecoxib is an oral,selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily). No statistically significant inhibition of COX-1 (assessed as ex vivo inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers.

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore

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possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulfonamides (e.g. thiazides, furosemide) but differs from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide antibiotics).

A dose dependent effect on TxB2 formation has been observed after high doses of celecoxib. However, in healthy subjects, in small multiple dose studies with 600 mg BID (three times the highest recommended dose) celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.
Several clinical studies have been performed confirming efficacy and safety in osteoarthritis and rheumatoid arthritis. Celecoxib was evaluated for the treatment of the inflammation and pain of OA of the knee and hip in approximately 4200 patients in placebo and active controlled trials of up to 12 weeks duration. It was also evaluated for treatment of the inflammation and pain of RA in approximately 2100 patients in placebo and active controlled trials of up to 24 weeks duration. Celecoxib at daily doses of 200mg - 400mg provided pain relief within 24 hours of dosing. Five randomised double-blind controlled studies have been conducted including scheduled upper gastrointestinal endoscopy in approximately 4500 patients free from initial ulceration (celecoxib doses from 50 mg-400 mg BID). In twelve week endoscopy studies celecoxib (100-800 mg per day) was associated with a significantly lower risk of gastroduodenal ulcers compared with naproxen (1000 mg per day) and ibuprofen (2400 mg per day). The data were inconsistent in comparison with diclofenac (150 mg per day). In two of the 12-week studies the percentage of patients with endoscopic gastroduodenal ulceration were not significantly different between placebo and celecoxib 200 mg BID and 400 mg BID.

In a prospective long-term safety outcome study (6 to 15 month duration, CLASS study), 5,800 OA and 2, 200 RA patients received celecoxib 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg TID or diclofenac 75 mg BID (both at therapeutic doses). Twenty-two percent of enrolled patients took concomitant low-dose acetylsalicylic acid (≤325 mg/day), primarily for cardiovascular prophylaxis. For the primary endpoint complicated ulcers (defined as gastrointestinal bleeding, perforation or obstruction) celecoxib was not significantly different than either ibuprofen or diclofenac individually. Also for the combined NSAID group there was no statically significant difference for complicated ulcers (relative risk 0,77, 95 % CI 0.41-1.46, based on entire study duration) . For the combined endpoint, complicated and symptomatic ulcers, the incidence was significantly lower in the celecoxib group compared to the NSAID group, relative risk 0.66, 95% CI 0.45-0.97 but not between celecoxib and diclofenac. Those patients on celecoxib and concomitant low-dose acetylsalicylic acid experienced 4 fold higher rates of complicated ulcers as compared to those on celecoxib alone. The incidence of clinically significant decreases in haemoglobin (>2 g/dL), confirmed by repeat testing, was significantly lower in patients on celecoxib compared to the NSAID group, relative risk 0.29, 95% CI 0.17- 0.48. The significantly lower incidence of this event with celecoxib was maintained with or without acetylsalicylic acid use.

5.2 Pharmacokinetic properties

Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption by about 1 hour.

Celecoxib is mainly eliminated by metabolism. Less than 1% of the dose is excreted unchanged in urine. The inter-subject variability in the exposure of celecoxib is about 10-fold. Celecoxib exhibits dose- and time-independent pharmacokinetics in the therapeutic dose range. Plasma protein binding is about 97% at therapeutic plasma concentrations and the drug is not preferentially bound to erythrocytes. Elimination half-life is 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment. Pharmacological activity resides in the parent drug. The main metabolites found in the circulation have no detectable COX-1 or COX-2 activity.

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Celecoxib is metabolised in the liver by hydroxylation, oxidation and some glucuronidation. The phase I metabolism is mainly catalysed by CYP2C9. There is a genetic polymorphism of this enzyme. Less than 1% of the population are poor metabolisers and have an enzyme with decreased activity. Plasma concentrations of celecoxib are probably markedly increased in such patients. Patients known to be CYP2C9 poor metabolisers should be treated with caution.
No clinically significant differences were found in PK parameters of celecoxib between elderly African-Americans and Caucasians.

The plasma concentration of celecoxib is approximately 100% increased in elderly women (>65 years).

Compared to subjects with normal hepatic function, patients with mild hepatic impairment had a mean increase in Cmax of 53% and in AUC of 26% of celecoxib. The corresponding values in patients with moderate hepatic impairment were 41% and 146% respectively. The metabolic capacity in patients with mild to moderate impairment was best correlated to their albumin values. Treatment should be initiated at half the recommended dose in patients with moderate liver impairment (with serum albumin 25-35g/L). Patients with severe hepatic impairment (serum albumin <25 g/l) have not been studied and celecoxib is contraindicated in this patient group.

There is little experience of celecoxib in renal impairment. The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients. Thus caution is advised when treating patients with renal impairment. Severe renal impairment is contraindicated.

5.3 Preclinical safety data

Conventional embryo-fetal toxicity studies resulted in dose dependent occurrences of diaphragmatic hernia in rat fetuses and of cardiovascular malformations in rabbit fetuses at systemic exposures to free drug approximately 5X (rat) and 3X (rabbit) higher than those achieved at the maximum recommended daily human dose (400mg). Diaphragmatic hernia was also seen in a peri-post natal toxicity study in rats, which included exposure during the organogenetic period. In the latter study, at the lowest systemic exposure where this anomaly occurred in a single animal, the estimated margin relative to the maximum recommended daily human dose was 3X.

In animals, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses. These effects are expected following inhibition of prostaglandin synthesis.

Celecoxib was excreted in rat milk. In a peri-post natal study in rats, pup toxicity was observed.

Based on conventional studies , genotoxicity or carcinogenicity, no special hazard for humans was observed, beyond those addressed in other sections of the SPC. In a two-year toxicity study an increase in nonadrenal thrombosis was observed in male rat at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules 100 mg contain lactose monohydrate, sodium lauryl sulphate, povidone K30, croscarmellose sodium and magnesium stearate. Capsule shells contain gelatin, titanium dioxide E171; ink contains indigotine E132.

Capsules 200 mg contain lactose monohydrate, sodium lauryl sulphate, povidone K30, croscarmellose sodium and magnesium stearate. Capsule shells contain gelatin, titanium dioxide E171; ink contains iron oxide E172.

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6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

Clear or opaque PVC/Aclar blisters or aluminium cold-formed blisters. Pack of 2, 6, 10, 20, 30, 40, 50, 60, 100, 10x10, 10x30, 10x50, 1x50 unit dose, 1x100 unit dose.

6.6 Instructions for use and handling, and disposal (if appropriate)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

{Name and address} *[Country name in the language of the text, NO telephone, fax numbers, e-mail addresses or websites.]*

8. MARKETING AUTHORISATION NUMBER(S)

[Item to be completed by the Marketing Authorisation Holder once the Marketing Authorisation has been granted.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Item to be completed by the Marketing Authorisation Holder once the Marketing Authorisation has been granted or renewed.]

10. DATE OF REVISION OF THE TEXT

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