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

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Prexige	100 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Prexige	200 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Prexige	400 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Lumiracoxib	100 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Lumiracoxib	200 mg	Film-coated tablet	Oral

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Lumiracoxib	400 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Frexocel	100 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Frexocel	200 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Frexocel	400 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Stellige	100 mg	Film-coated tablet	Oral

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Stellige	200 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Stellige	400 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Exforge	100 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Exforge	200 mg	Film-coated tablet	Oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Exforge	400 mg	Film-coated tablet	Oral

ANNEX II

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

SCIENTIFIC CONCLUSIONS FOR THE AMENDMENT OF THE MARKETING AUTHORISATION

In September 2004, the Marketing Authorisation Holder (MAH) of rofecoxib (a selective Cox-2-inhibitor) informed the EMEA that new clinical trial (APPROVe) data for rofecoxib have revealed a risk of thrombotic cardiovascular (CV) events. These data resulted in the worldwide withdrawal of Vioxx (rofecoxib) from the market on 30 September 2004 by the MAH and raised questions regarding the cardiovascular safety of other Cox-2 inhibitors.

Further to discussions at the CHMP October 2004 plenary meeting, the European Commission recommended that this public health issue on all aspects of cardiovascular safety including thrombotic events and cardio-renal events is the subject of Community referrals under Article 31 of Directive 2001/83/EC, as amended regarding decentrally authorised products containing celecoxib, etoricoxib and lumiracoxib and subject to a review procedure under Article 18 of Council Regulation (EEC) No 2309/93, as amended regarding the centrally authorised products containing celecoxib (Onsenal), parecoxib (Dynastat/Rayzon) and valdecoxib (Bextra/Valdyn), which were started in November 2004.

During the CHMP meeting of February 2005, discussions on cardiovascular safety took place. The CHMP agreed that an Urgent Safety Restriction (USR) on cardiovascular safety was needed to introduce new contraindications and strengthen warnings and information on side effects in the SPC. This USR was initiated on 16 February 2005 and finalised on 17 February 2005.

On 7 April 2005, the FDA (Food and Drug Administration) and the EMEA requested that Pfizer voluntarily withdraw Bextra (valdecoxib) from the market and Pfizer agreed to suspend sale and marketing of Bextra worldwide pending further discussions on the unfavorable risk versus benefit due to data on serious skin reactions.

On 20 April 2005, Pfizer presented data on serious skin reactions for valdecoxib during a hearing.

Further to a request from the European Commission, the scope of the ongoing class was broadened review to include the assessment of serious skin reactions in addition to the cardiovascular safety aspects.

Between November 2004 and June 2005, the MAH made an oral explanation to the CHMP on cardiovascular and skin safety aspects for lumiracoxib on 18 January 2005.

On 23 June 2005, the CHMP concluded that:

- Further to the assessment of:

    - the new data provided on rofecoxib by the APPROVe clinical study, which revealed a risk of thrombotic CV events,
    - the data on celecoxib presented in the APC study, which suggested a dose-related increased risk of serious CV events,
    - the data on valdecoxib and parecoxib presented in the CABG (Coronary Artery Bypass Graft) and in the CABG II studies, which showed a higher rate of serious CV thromboembolic events in the parecoxib/valdecoxib treatment arm compared to the group of patients receiving placebo,
    - the data on etoricoxib in the EDGE study and pooled analyses of other clinical trials, which suggested an association with a higher thrombotic risk than naproxen,
    - the data on lumiracoxib in the Target study, which suggested a small increase in thrombotic events (especially myocardial infarction) versus naproxen,

all available data show an increased risk of CV adverse reactions for Cox-2 inhibitors as a class and agreed that there is an association between duration and dose of intake and the probability of suffering a CV reaction.

▪ Further to the assessment of the data on serious skin reactions, lumiracoxib does not appear to be associated with an unusually large number of reports of serious skin reactions. There were no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme reported in association with the use of lumiracoxib. However, exposure is limited to clinical trials.

The CHMP confirmed changes to the Product Information already introduced through a type II variation adopted in May 2005 and requested further changes.

The changes of the Product Information related to the CV can be summarised as follows:

- Addition of a statement that decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.
- Addition of a statement that prescribers should use the lowest effective dose, for the shortest possible duration, and that the need for pain relief should be re-evaluated frequently.
- Addition of the contraindications *Established ischaemic heart disease and/or cerebrovascular disease* and *Peripheral arterial disease*.
- Addition of a warning on clinical trials which suggest that selective Cox-2 inhibitors may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs.
- Addition of a warning for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking.
- Addition of a warning for prescribers to consider discontinuation of therapy if during treatment, patients deteriorate in any of the organ system functions described.
- Addition of a warning for prescribers to exercise caution when prescribing NSAIDs, in combination with ACE inhibitors or angiotensin II receptor antagonists.

The changes of the Product Information related to the SCAR can be summarised as follows:

- Addition of a warning to report that the onset of skin reactions occur in the majority of cases within the first month of treatment.
- Addition of a warning for patients with a history of any drug allergy.
- Addition of a warning to highlight that fatal serious skin reactions have now occurred with Cox-2 inhibitors.
- Addition of a detailed description of the first signs of skin reactions leading to discontinuation of the treatment.

GROUNDS FOR THE AMENDMENT OF THE MARKETING AUTHORISATION

Whereas, the CHMP

- is of the Opinion that the benefit/risk balance of medicinal products containing lumiracoxib in the agreed indications remains favourable and the Marketing Authorisations should be maintained according to revised Summaries of Product Characteristics (attached in Annex III of the CHMP Opinion),
- concluded that the cardiovascular safety and serious skin reactions should be continuously and carefully monitored and assessed,
- recommended follow up measures to further investigate the safety of lumiracoxib.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 31 referral for lumiracoxib containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

{INVENTED NAME} 100 mg film-coated tablets
{INVENTED NAME} 200 mg film-coated tablets
{INVENTED NAME} 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg film-coated tablet contains 100 mg lumiracoxib.
Each 200 mg film-coated tablet contains 200 mg lumiracoxib.
Each 400 mg film-coated tablet contains 400 mg lumiracoxib.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

100 mg film-coated tablets: Ovaloid, red, tablets with “NVR” debossed on one side and “OB” on the other side.

200 mg film-coated tablets: Ovaloid, red, tablets with “NVR” debossed on one side and “OC” on the other side.

400 mg film-coated tablets: Ovaloid, red, tablets with “NVR” debossed on one side and “OD” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis.

For the short-term relief of moderate to severe acute pain associated with:
- primary dysmenorrhea,
- dental surgery,
- orthopaedic surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient’s overall risks (see section 4.3 and 4.4).

4.2 Posology and method of administration

{Invented Name} film-coated tablets are administered orally and may be taken with or without food.

Osteoarthritis
The recommended starting dose is 100 mg once daily. In patients who fail to respond, the dose may be increased to 200 mg daily in one or two divided doses. Patients should not exceed this dose. The maximum treatment duration in clinical studies was 12 months.

Acute pain
The recommended dose is 400 mg once daily. Patients should not exceed this dose and the treatment duration should not exceed 5 days.

Relief of acute pain due to dental surgery: the maximum treatment duration in clinical studies was 24 hours.

Relief of acute pain due to orthopaedic surgery: the maximum treatment duration in clinical studies was 5 days.

Relief of pain due to primary dysmenorrhea: the maximum treatment duration in clinical studies was 3 days.

As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Ethnic differences: Dosing recommendations are the same for Asians, Blacks and Caucasians (see section 5.2).

Elderly: As with other drugs used in the elderly, it is prudent to initiate treatment with the lower recommended dose. Caution should be exercised in elderly osteoarthritis patients when increasing from a 100 mg to a 200 mg daily dose (see section 4.4 and 5.2).

CYP2C9 poor metabolisers: No dose adjustment is necessary in patients known to be CYP2C9 poor metabolisers (see section 5.2).

Hepatic impairment: No dose adjustment is necessary for patients with mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-8) hepatic impairment. However, it is prudent to initiate treatment at the lower recommended dose in such patients (see section 4.3, 4.4 and 5.2).

Renal insufficiency: No dose adjustment is necessary for patients with creatinine clearance ≥50 ml/min. Lumiracoxib is contraindicated in patients with moderate to severe renal impairment (estimated creatinine clearance ≤50 ml/min) (see section 4.3, 4.4 and 5.2).

Paediatric use: {Invented Name} has not been studied in children and thus is contraindicated in children under 18 years of age.

4.3 Contraindications

- Known hypersensitivity to lumiracoxib or to any of the excipients.
- Patients who have experienced asthma, acute rhinitis, nasal polyps, angioedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs.
- Patients with active peptic ulceration or gastrointestinal bleeding.
- Patients with inflammatory bowel disease.
- Patients with congestive heart failure (NYHA II-IV).
- Patients with established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Patients with moderate to severe renal dysfunction (estimated creatinine clearance <50 ml/min).
- Patients with severe hepatic disease (Child-Pugh ≥9).
- Third trimester of pregnancy and breast feeding (see section 4.6 and 5.3).
- Patients under 18 years of age.

4.4 Special warnings and special precautions for use

GI effects
Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in a fatal outcome, have occurred in patients treated with lumiracoxib. In clinical studies, few patients (<0.3%) treated with lumiracoxib developed perforations, obstruction or bleeds (POBs).

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 ASA concomitantly, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when lumiracoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see section 5.1).

Renal effects
Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of lumiracoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function.

Patients at greatest risk of this response are those with pre-existing renal dysfunction, uncompensated heart failure, or cirrhosis and those receiving diuretics or ACE inhibitors. Monitoring of renal function in such patients should be considered. Caution should be used when initiating treatment with lumiracoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with lumiracoxib.

Hypertension and oedema
As with other drugs known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking lumiracoxib in clinical trials. Therefore, lumiracoxib 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. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of lumiracoxib should be taken.

Medically appropriate supervision should be maintained when using lumiracoxib in the elderly and in patients with mild renal, hepatic, or cardiac dysfunction.

Hepatic effects
Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), greater than three times the upper limit of normal (>3xULN) have been reported in placebo/active-controlled clinical studies in approximately 1.2% of patients in clinical trials up to one year with lumiracoxib 100 mg and 200 mg daily. Marked elevations (>8xULN) have been observed in 0.3% with 100 mg once or twice daily and 0.6% of patients at 200 mg once daily.

Chronic use with 400 mg daily dose was associated with more frequent and more marked elevations in ALT/AST. In a long-term controlled study with lumiracoxib 400 mg daily, rare cases of hepatitis have been reported (see section 4.8).

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if abnormal liver function tests (ALT or AST>3xULN) persist, lumiracoxib should be discontinued.

Cardiovascular effects
COX-2 selective inhibitors are not a substitute for ASA for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued (see section 4.5 and 5.1).

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI)and stroke), relative to placebo and some NSAID's. As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patients need

for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see section 4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (eg hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with lumiracoxib after careful consideration (see section 5.1).

Skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance. Patients appear to be at highest risk for these reactions early in the course of therapy, with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving lumiracoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Lumiracoxib, should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General
If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of lumiracoxib therapy should be considered.

Use of lumiracoxib, as with any drug known to inhibit COX-2, is not recommended in women attempting to conceive (see section 4.6).

As with other NSAIDs, lumiracoxib may mask fever and other signs of inflammation or infection.

{Invented Name} 100 mg and 200 mg film-coated tablets contain lactose (23.3 mg and 46.6 mg, respectively). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take 100 mg and 200 mg film-coated tablets. However, there is no lactose in {Invented Name} 400 mg film-coated tablets.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions

Oral anticoagulants: In a drug-drug interaction study in healthy subjects stabilised on warfarin therapy, the administration of lumiracoxib 400 mg once daily for five days was associated with an approximate 15% increase in prothrombin time. Therefore anticoagulant activity should be monitored in patients taking warfarin or similar agents, particularly in the first few days after initiating or changing the dose of lumiracoxib.

Diuretics, ACE inhibitors and Angiotensin II antagonists: NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal functions), the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be given consideration in patients taking lumiracoxib concomitantly with ACE-inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Other NSAIDs: Lumiracoxib can be used with low-dose aspirin. Concomitant administration of lumiracoxib with high doses of aspirin, other NSAIDs or COX-2 inhibitors should be avoided.

Ciclosporin or tacrolimus: Although this interaction has not been studied with lumiracoxib, co-administration of ciclosporin or tacrolimus and any NSAID may increase the nephrotoxic effect of ciclosporin or tacrolimus. Renal function should be monitored when lumiracoxib and either of these drugs is used in combination.

Pharmacokinetic Interactions

The oxidative metabolism of lumiracoxib is mainly CYP2C9 mediated. *In vitro* studies indicate that lumiracoxib is not a significant inhibitor of other cytochrome P450 isoforms, including CYP1A2, CYP2C8, CYP 2C19, CYP2D6, CYP2E1, and CYP3A4. Based on these studies, lumiracoxib appears to have a low potential for interactions with compounds cleared by cytochrome P450 except for CYP2C9 where there is possibility of decreased clearance of concomitantly administered substrates of CYP2C9.

In vivo studies suggest that lumiracoxib has low potential for interactions with CYP2C9 substrates. However care should be exercised when lumiracoxib is co-administered with substrates of CYP2C9 that have very narrow therapeutic index, such as phenytoin and warfarin.

Based on *in vitro* studies, interactions involving plasma protein binding are not expected to have any clinically relevant effects on lumiracoxib or co-administered drugs.

The effect of lumiracoxib on the PK of other drugs
Warfarin: In a study with warfarin, which is considered to be a CYP2C9 substrate sensitive to drug interactions, co-administration with lumiracoxib 400 mg had no effect on plasma AUC, Cmax or Tmax of R-warfarin or S-warfarin. Compared to placebo treatment, recovery of the S-7-OH warfarin metabolite in urine was about 25% lower in subjects treated with lumiracoxib.

Methotrexate: Co-administration of lumiracoxib at doses of 400 mg once daily had no clinically significant effects on the plasma pharmacokinetics, plasma protein binding or urinary excretion of methotrexate and of the 7-hydroxy methotrexate metabolite.

Oral contraceptives: Co-administration of lumiracoxib did not affect the steady state pharmacokinetics or the efficacy of ethinylestradiol and of levonorgestrel. Thus no alteration in oral contraceptive medication is necessary when lumiracoxib is co-administered.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus when lumiracoxib and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Effects of other drugs on the PK of lumiracoxib
Fluconazole: Co-administration of lumiracoxib with the potent CYP2C9 inhibitor fluconazole had no clinically relevant effect on the pharmacokinetics or the COX-2 selectivity of lumiracoxib.

Omeprazole: Omeprazole had no effect on the pharmacokinetics of lumiracoxib.

Antacids: (aluminium hydroxide/magnesium hydroxide) had no clinically relevant effect on the pharmacokinetics of lumiracoxib.

4.6 Pregnancy and lactation

Pregnancy
The use of lumiracoxib, as with any drug to inhibit COX-2, is not recommended in women attempting to conceive.

The use of lumiracoxib is contraindicated in the last trimester of pregnancy because, as with other drugs known to inhibit prostaglandin synthesis, it may cause uterine inertia and premature closure of the ductus arteriosus.

The use of lumiracoxib in pregnant women has not been studied in adequate and well controlled clinical trials and therefore it should not be used during the first two trimesters of pregnancy unless the potential benefit to the patients justifies the potential risk to the fetus.

Breast-feeding mothers
It is not known whether lumiracoxib is excreted in human milk. Lumiracoxib is excreted in the milk of lactating rats. Women who use lumiracoxib should not breastfeed.

4.7 Effects on ability to drive and use machines

No studies on the effect of lumiracoxib on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence while taking lumiracoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

In clinical trials, lumiracoxib was evaluated for safety in approximately 7,000 patients, including approximately 4,000 patients with OA and 2,100 patients with RA (approximately 1,100 patients with OA or RA were treated for 6 month, and 530 patients with OA were treated for 1 year).

In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients with OA or RA treated with lumiracoxib 200 mg daily for up to one year (approximately 920 patients for three months and approximately 250 patients for one year).

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

Infections
Common: influenza like symptoms, respiratory tract infection (e.g bronchitis), urinary tract infection
Uncommon: candidiasis, ear infection, herpes simplex, tooth infection

Blood and lymphatic system disorders
Uncommon: anaemia
Rare: pancytopenia, neutropenia, leucopenia

Psychiatric disorders
Uncommon: depression, insomnia, anxiety

Nervous system disorders
Common: dizziness, headache
Uncommon: syncope, hypoaesthesia, migraine, paraesthesia, dysgeusia, vertigo, tinnitus

Eye disorders
Uncommon: conjunctivitis, dry eye, visual disturbance (e.g. blurred vision)
Rare: keratitis

Cardiac disorders
Uncommon: palpitations, myocardial infarction*
Rare: cardiac failure, atrioventricular block of first degree
Vascular disorders
Uncommon: venous insufficiency, hypotension, cerebrovascular accident*

Respiratory disorders
Common: cough, pharyngitis
Uncommon: dyspnoea, epistaxis, rhinitis, sinus congestion, asthma

Gastrointestinal disorders
Common: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, flatulence
Uncommon: gastroduodenal ulcer, gastroduodenitis, oesophagitis, abdominal distension, aphthous stomatitis, dry mouth, dysphagia, epigastric discomfort, eructation, gastrooesophageal reflux disease, gingivitis, hyperacidity, toothache
Rare: gastrointestinal haemorrhage

Hepatobiliary disorders
Rare: cholecystitis, cholelithiasis, hepatitis

Skin and subcutaneous tissue disorders
Uncommon: contusion, exanthem, pruritus, rash, urticaria
Rare: angioedema

Musculoskeletal disorders
Uncommon: joint swelling, muscle cramps, arthralgia

Renal and urinary disorders
Uncommon: dysuria, urinary frequency, cystitis
Rare: chromaturia, renal failure

Reproductive system disorders
Rare: erectile dysfunction

General disorders
Common: fatigue, oedema (e.g lower limb)
Uncommon: appetite increased or decreased, chest pain, rigors, thirst
Rare: anaphylaxis

Investigations
Uncommon: alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood urea increased, gamma-glutamyltransferase increased, weight increased.
Rare: blood bilirubin increased, blood glucose increased

* Based on analyses of long-term placebo and active controlled clinical trials, some selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke. The absolute risk increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).

Approximately 1,100 patients were treated with lumiracoxib in analgesia clinical studies (post-surgical dental pain, primary dysmenorrhea, and post-orthopedic surgery pain). The undesirable effects profile was generally similar to that reported in the OA and RA studies. In the post-orthopedic surgery pain studies, anemia was reported more frequently, although the frequency was similar to placebo.

The following rare serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for lumiracoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse effects and severe skin reactions.

Compared to a daily dose of 200 mg, a daily dose of 400 mg of lumiracoxib is associated with a relatively higher frequency of drug-related adverse events, especially the gastrointestinal, neurological and psychiatric events.

4.9 Overdose

There is no clinical experience of overdose. Multiple doses of lumiracoxib 1,200 mg once daily have been administered to patients with rheumatoid arthritis for 4 weeks 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.

Haemodialysis is unlikely to be an efficient method of drug removal due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs, ATC code: M01 AH 06

Mode of Action
Lumiracoxib is an orally active, selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range.

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 possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established. Across clinical pharmacology studies, lumiracoxib produced dose-dependent inhibition of COX-2 in plasma without inhibition of COX-1. Selective inhibition of COX-2 by lumiracoxib provides anti-inflammatory and analgesic effects. Administration of 100 mg, 200 mg or 400 mg once daily leads to >90% peak inhibition of COX-2. There is no significant inhibition of COX-1 (assessed as *ex vivo* inhibition of thromboxane B_2) up to 800 mg in healthy volunteers. Lumiracoxib at 800 mg daily did not lead to clinically meaningful inhibition of gastric prostaglandin synthesis and had no effect on platelet function.

Efficacy
In patients with osteoarthritis, lumiracoxib doses up to 200 mg once daily provided significant improvements in pain, stiffness, function, and patient assessments of disease status. These beneficial effects were maintained for up to 52 weeks. There is no additional benefit by increasing the dose to 400 mg daily.

In clinical studies, lumiracoxib 400 mg relieved pain in acute analgesic models of post-operative dental pain, post-orthopaedic surgical pain, and primary dysmenorrhea. In single dose post-operative dental pain trials, the onset of analgesia occurred within 45 minutes and persisted for as long as 24 hours after dosing. In short-term, multiple-dose clinical studies of post-orthopaedic surgical pain and pain from primary dysmenorrhea, lumiracoxib 400 mg once daily was effective in relieving pain.

Safety
The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)

TARGET, a 12-month, double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg once daily (two to four times the recommended OA dose), naproxen 500 mg twice daily or ibuprofen 800 mg three times daily. TARGET included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24% of patients in the overall study population) and age.

Gastrointestinal Effect in TARGET (12-month study)

The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs).

- In the population not using low-dose aspirin, the incidence of POBs was 14/6950 patients (0.2%) for lumiracoxib versus 64/6968 patients (0.92%) for NSAIDs, with a hazard ratio (HR) of 0.21 [95% CI 0.12-0.37] p<0.0001.
- In the low dose ASA group the incidence of POBs was 15/2167 patients (0.69%) for lumiracoxib versus 19/2159 patients (0.88%) for NSAIDs, with a HR of 0.79 [95% CI 0.40-1.55] (not statistically significant).
- In the overall population, the incidence of POBs was 29/9117 patients (0.32%) for lumiracoxib versus 83/9127 patients (0.91%) for NSAIDs, with a HR of 0.34 [95% CI 0.22-0.52] p<0.0001.

Cardiovascular Effect in TARGET (12-month study)

The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint: confirmed or probable myocardial infarction (clinical or silent), stroke (ischemic or haemorrhagic) and CV death. There were no significant differences between lumiracoxib and NSAIDs. However, the APTC event rate was numerically higher for lumiracoxib than for naproxen but lower than for ibuprofen.

- In the population not using low-dose aspirin, the incidence of APTC events was 35/6950 patients (0.50%) for lumiracoxib versus 27/6968 patients (0.39%) for NSAIDs, with a HR of 1.22 [95% CI 0.74-2.02] p=0.4343. When compared separately to ibuprofen and naproxen, the HR were 0.94 [95% CI 0.44-2.04] p=0.8842 and 1.49 [95% CI 0.76-2.92] p=0.2417, respectively.
- In the low-dose ASA group, the incidence of APTC events was 24/2167 patients (1.11%) for lumiracoxib versus 23/2159 patients (1.07%) for NSAIDs, with a hazard ratio (HR) of 1.04 [95% CI 0.59-1.84] p=0.8918. When compared separately to ibuprofen and naproxen, the HR were 0.56 [95% CI 0.20-1.54] p=0.2603 and 1.42 [95% CI 0.70-2.90] p=0.3368, respectively.
- In the overall population, the incidence of APTC events was 59/9117 patients (0.65%) for lumiracoxib versus 50/9127 patients (0.55%) for NSAIDs, with a HR of 1.14 [95% CI 0.78-1.66] p=0.5074. When compared separately to ibuprofen and naproxen, the HR were 0.76 [95% CI 0.41-1.40] p=0.3775 and 1.46 [95% CI 0.89-2.37] p=0.1313, respectively.

MI events in TARGET (12-month study)

There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of MI (clinical MI and silent MI).

- In the population not using low-dose aspirin, the incidence of MI events was 14/6950 patients (0.20%) for lumiracoxib versus 9/6968 patients (0.13%) for NSAIDs, with a HR of 1.47 [95% CI 0.63-3.39] p=0.3706. When compared separately to ibuprofen and naproxen, the HR were 0.75 [95% CI 0.20-2.79] p=0.6669 and 2.37 [95% CI 0.74-7.55] p=0.1454, respectively.
- In the low-dose ASA group, the incidence of MI events was 9/2167 patients (0.42%) for lumiracoxib versus 8/2159 patients (0.37%) for NSAIDs, with a HR of 1.14 [95% CI 0.44-2.95] p=0.7899. When compared separately to ibuprofen and naproxen, the HR were 0.47 [95% CI 0.04-5.14] p=0.5328 and 1.36 [95% CI 0.47-3.93] p=0.5658, respectively.
- In the overall population, the incidence of MIs was 23/9117 patients (0.25%) for lumiracoxib versus 17/9127 patients (0.19%) for NSAIDs, with a HR of 1.31 [95% CI 0.70-2.45] p=0.4012. When compared separately to ibuprofen and naproxen, the HR were 0.66 [95% CI 0.21-2.09] p=0.4833 and 1.77 [95% CI 0.82-3.84] p=0.1471, respectively.

The cardiovascular safety of lumiracoxib beyond 1 year of use has not been established.

Cardiorenal effect in TARGET (12-month study)

For systolic blood pressure, mean change from baseline were +0.4 mmHg for lumiracoxib and +2.1 mmHg for NSAIDs ($p<0.0001$). For diastolic blood pressure, mean change from baseline were -0.1 mmHg for lumiracoxib and +0.5 mmHg for NSAIDs ($p<0.0001$). The number of discontinuations in TARGET due to oedema was not significantly different between lumiracoxib (43) and NSAIDs (55). The number of discontinuations due to hypertension-related events was also not significantly different between lumiracoxib (37) and NSAIDs (52).

5.2 Pharmacokinetic properties

Absorption
Lumiracoxib is rapidly absorbed following oral administration. At 15 minutes post 400 mg dose, the plasma concentration reached 0.6 µg/ml, which is sufficiently high to achieve over 90% inhibition of COX-2. Median t_{max} is about 2 hours post dose. Over the range of 25 to 800 mg, extent of exposure (AUC) increases in a dose-proportional manner and the peak plasma concentration (C_{max}) was roughly dose-proportional. Following 400 mg once daily dosing, C_{max} was about 9 µg/ml and AUC was about 31 µg h/ml.

The absolute bioavailability of lumiracoxib is approximately 74%.

Food had no significant effect on either C_{max} or AUC of lumiracoxib when either 200 mg or 400 mg film-coated tablets of {Invented Name} were taken with a high-fat meal. {Invented Name} film-coated tablets can be administered without regard to timing of meals.

Distribution
Lumiracoxib is highly bound to plasma proteins, (≥98%), and binding is independent of concentration over a range of 0.1 to 100 µg/mL.

The volume of distribution (Vss) is 9 L.

By about 5 hour post dose, concentrations of lumiracoxib in human synovial fluid of rheumatoid arthritis patients were higher than plasma and remained substantially higher for the remainder of the dose interval (AUC_{12-24} in synovial fluid was 2.6 times higher than that for plasma). No difference was observed in the extent of lumiracoxib protein binding in synovial fluid compared to plasma.

Lumiracoxib crosses the placenta in rats and rabbits.

One hour after oral administration of ^{14}[C]-labeled lumiracoxib in a rat model of inflammation, the ratio of radioactivity detected at the site of inflammation versus that detected in the blood was 2:1, and was 8:1 four hours post dose. This indicates lumiracoxib and/or its metabolites are preferentially distributed and retained in inflamed tissue.

Biotransformation
In humans, lumiracoxib undergoes extensive hepatic metabolism. The oxidative metabolism of lumiracoxib is mainly CYP2C9 mediated.

Of the total drug related material in plasma, unchanged lumiracoxib is the major component. Three major metabolites were identified in plasma: 4'-hydroxy-lumiracoxib, 5-carboxy-lumiracoxib and 4'-hydroxy-5-carboxy-lumiracoxib. In addition various conjugates (glucuronides and sulfates) of these metabolites are formed. The 4'-hydroxy metabolite has similar potency and COX-2 selectivity to lumiracoxib.

The concentration of 4'-hydroxy metabolite in plasma and synovial fluid is low, thus it is unlikely to contribute to efficacy. Other metabolites are not active as COX-1 or COX-2 inhibitors.

Elimination
Lumiracoxib is eliminated predominantly via hepatic metabolism. After administration of a single dose of lumiracoxib 400 mg to healthy subjects, 54% of drug-related material was excreted in urine

and 43% in feces. Only about 5% of the administered dose was recovered in excreta as unchanged lumiracoxib.

Plasma clearance is 7.7 L/h.

The mean plasma half-life of lumiracoxib is approximately 4 hours. Lumiracoxib does not accumulate in plasma under once or twice daily administration and steady state is achieved on the first day of administration with no increase in C_{max} or AUC after extended dosing.

Characteristics in patients

Gender:
There is no difference in exposure of lumiracoxib in men and women.

Elderly:
In elderly subjects (over 65 years old), a 15% increase in AUC was observed as compared to younger subjects. Dosage adjustment in the elderly is not necessary.

Race:
The pharmacokinetics of lumiracoxib are similar in Asians, Blacks and Caucasians.

CYP2C9 polymorphism:
On the basis of both plasma exposure to lumiracoxib and pharmacogenetic analysis, no evidence has been found to suggest that exposure to lumiracoxib is increased in subjects with genotypes of CYP2C9 associated with reduced metabolic clearance. No dose adjustment is necessary in patients known to be CYP2C9 poor metabolisers.

Hepatic Insufficiency:
Compared to healthy subjects, exposure to lumiracoxib was not changed in patients with moderate hepatic impairment (Child-Pugh score 7-8). No difference was observed in the plasma protein binding between the two groups. Thus, no dose adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of lumiracoxib have not been studied in patients with severe hepatic impairment (Child-Pugh $\geq$9).

Renal Insufficiency:
When lumiracoxib was administered to patients with end-stage renal disease, a 33% decrease in lumiracoxib C_{max} and a 27% decrease in AUC were observed compared to healthy subjects. Mean exposure to the active 4'-hydroxy-lumiracoxib metabolite was largely unaffected. Plasma protein binding of lumiracoxib was similar in healthy subjects and in patients with end-stage renal disease. Dialysis has no effect on the exposure of patients to lumiracoxib or its active metabolite. Thus no dose adjustment is necessary in patients with renal impairment. While renal insufficiency does not significantly influence the pharmacokinetics of lumiracoxib and its active metabolite, use of lumiracoxib in patients with moderate to severe renal insufficiency is contraindicated because of potential further deterioration of renal function due to cyclooxygenase inhibition (see section 4.3 and 4.4).

Hypertensive Patients:
Lumiracoxib did not affect blood pressure control in hypertensive patients, nor did it differ from placebo regarding newly occurring hypertension in clinical trials.

Paediatric patients:
The pharmacokinetics of lumiracoxib in paediatric patients have not been studied.

5.3 Preclinical safety data

In preclinical studies, lumiracoxib has been demonstrated to be neither mutagenic nor carcinogenic. Chromosome aberrations were induced in V79 cells at high, cytotoxic concentrations of lumiracoxib,

which are not considered to have biological relevance for humans. There was no indication of genotoxic potential in three *in vivo* rat studies (micronucleus tests in bone marrow and liver and liver comet assay).

In repeat dose toxicity studies in rats and monkeys, target organs were the gastrointestinal tract and kidney. Systemic exposure at levels with no adverse effect for these targets in rat (26-week study) and monkey (39-week study) were 6.5 and 22 times that in man following a 200 mg therapeutic dose, respectively.

Lumiracoxib was not teratogenic in reproduction toxicity studies conducted in rats and rabbits at doses representing systemic exposure 10.4 (rat) and 38 (rabbit) times greater than the human therapeutic level after a 200 mg dose. In rats the incidence of pre-implantation loss was increased at a dose of 100 mg/kg/day, (10.4 times the human therapeutic exposure following a dose of 200 mg), which caused maternal toxicity.

The incidence of resorption was increased in rabbits at approximately 9 times the human exposure following a 200 mg dose. At the level with no embryo/fetal effect, the systemic exposure was 8.6 (rat) and 2.2 (rabbit) times that in man following a 200 mg therapeutic dose. In a pre- and post-natal development study in rats, an increase in stillborn pups and reduced embryo/fetal survival was seen at maternally toxic doses ≥3 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets 100 mg:
Core:
Cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide, magnesium stearate

Coating:
Hypromellose, Macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171)

Film-coated tablets 200 mg:
Core:
Cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide, magnesium stearate

Coating:
Hypromellose, Macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171)

Film-coated tablets 400 mg:
Core:
Cellulose microcrystalline, croscarmellose sodium, povidone, magnesium stearate

Coating:
Hypromellose, Macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Clear PVC/aluminium blisters in packs containing 2, 4, 5, 6, 10, 20, 30, 50, 100, or 600 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00101/0677

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th September 2003

10. DATE OF REVISION OF THE TEXT

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

Follow-up measures of the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below:

Area	**Description**
Clinical 1	To develop and disseminate a Physician Decision Treatment Guide for prescribers of lumiracoxib.
Clinical 2	To conduct physician surveys to monitor appropriate use.
Clinical 3	To support multiple venues for healthcare professionals including prescribers and pharmacists.
Clinical 4	To conduct a Prescription Event Monitoring study.
Clinical 5	To conduct a database study of drug utilisation of lumiracoxib and other marketed NSAIDs and COX-2 inhibitors.
Clinical 6	Expedited reporting of a list of agreed SAEs.
Clinical 7	To monitor and report PSUR of a list of agreed AEs.