\

Agreed Core Safety Profile

Active Substance:	Celecoxib
Brand Names:	Celebrex, Celebra, Solexa, Celora, Aclarex, Artilog
Pharmaceutical form(s)/strength:	Capsule, hard, 100 mg and 200 mg
RMS:	Sweden
Date:	25 September 2012
Supersedes:	n/a

4.2. Posology and method of administration

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible 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 (4.3, 4.4, 4.8 and 5.1).

*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 dose of 200 mg twice daily may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Rheumatoid arthritis: The initial recommended daily dose is 200 mg taken in two divided doses. The dose may, if needed, later be increased to 200 mg twice daily. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Ankylosing Spondylitis: The recommended daily dose is 200 mg taken once daily or in two divided doses. In a few patients, with insufficient relief from symptoms, an increased dose of 400 mg once daily or in two divided doses may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

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

Celexocib may be taken with or without food.

Elderly: (>65 years) As in younger adults, 200 mg per day should be used initially. The dose may, if needed, later be increased to 200 mg twice daily. Particular caution should be exercised in elderly with a body weight less than 50 kg. (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.

CYP2C9 Poor Metabolizers: Patients who are known, or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the dose to half the lowest recommended dose. (See 5.2)

4.3. Contraindications

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

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 creatinine clearance <30 ml/min.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4. Special warnings and special precautions for use

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 further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib 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 5.1).

The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.

Increased number of serious cardiovascular events, mainly myocardial infarction, has been found in a long-term placebo-controlled study in subjects with sporadic adenomatous polyps treated with celecoxib at doses of 200 mg BID and 400mg BID compared to placebo (see 5.1).

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible 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 (4.2, 4.3, 4.8 and 5.1).

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).

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.

As with all NSAIDS, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Therefore, blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

NSAIDs, including celecoxib, may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients

at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.

Some cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis and, hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib treatment (see 4.8).

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

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, 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 celecoxib (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving celecoxib (see 4.8). Patients with a history of sulphonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see 4.3). Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other 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).

Celecoxib 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 medicinal products. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics, or elderly patients) when ACE inhibitors or angiotensin II receptor antagonists are combined with NSAIDs, including celecoxib. 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.

In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients treated with celecoxib 200 mg BID, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients treated with placebo; this difference was statistically significant.

Coadministration of NSAIDs and ciclosporin or tacrolimus have been suggested to increase the nephrotoxic effect of ciclosporin 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 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 200 mg twice daily with 450 mg 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
In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors could result in further increases in celecoxib exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers (see sections 4.2 and 5.2).

Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200 mg single dose of celecoxib and 200 mg 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.

Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Administration of celecoxib to a limited number of lactating women has shown a very low transfer of celecoxib into breast milk. 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

Adverse reactions are listed by system organ class and ranked by frequency in **Table 1**, reflecting data from the following sources:

- Adverse reactions reported in osteoarthritis patients and rheumatoid arthritis patients at incidence rates greater than 0.01% and greater than those reported for placebo during 12 placebo- and/or active-controlled clinical trials of duration up to 12 weeks at celecoxib daily doses from 100 mg up to 800 mg. In additional studies using non-selective NSAID comparators, approximately 7400 arthritis patients have been treated with celecoxib at daily doses up to 800 mg, including approximately 2300 patients treated for 1 year or longer. The adverse reactions observed with celecoxib in these additional studies were consistent with those for osteoarthritis and rheumatoid arthritis patients listed in **Table 1**.
- Adverse reactions reported at incidence rates greater than placebo for subjects treated with celecoxib 400 mg daily in long-term polyp prevention trials of duration up to 3 years (the APC and PreSAP trials; see Section 5.1, Pharmacodynamic properties: Cardiovascular Safety – Long-Term Studies Involving Patients With Sporadic Adenomatous Polyps).
- Adverse drug reactions from post-marketing surveillance as spontaneously reported during a period in which an estimated >70 million patients were treated with celecoxib (various doses, durations, and indications). Because not all adverse drug reactions are reported to the MAH and included in the safety database, the frequencies of these reactions cannot be reliably determined.

Table 1. Adverse Drug Reactions in Celecoxib Clinical Trials and Surveillance Experience (MedDRA Preferred Terms)[1,2]

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10,000 to <1/1000)	**Frequency Not Known** (Post-marketing experience)[3]
Infections and infestations	Sinusitis, upper respiratory tract infection, urinary tract infection			
Blood and lymphatic system disorders		Anemia	Leucopenia, thrombocytopenia	Pancytopenia
Immune system disorders	Allergy aggravated			Serious allergic reactions, anaphylactic shock, anaphylaxis
Metabolism and nutrition disorders		Hyperkaelemia		
Psychiatric disorders	Insomnia	Anxiety, depression, tiredness	Confusion	Hallucinations
Nervous system disorders	Dizziness, hypertonia	Paraesthesia, somnolence, cerebral infarction[1]	Ataxia, taste alteration	Headache, aggravated epilepsy, meningitis aseptic, ageusia, anosmia, fatal intracranial haemorrhage
Eye disorders		Blurred vision		Conjunctivitis, ocular

				haemorrhage, retinal artery or vein occlusion
Ear and labyrinth disorders		Tinnitus, hypoacusis[1]		
Cardiac disorders	Myocardial infarction[1]	Heart failure, palpitations, tachycardia		Arrhythmia
Vascular disorders				
Hyper-tension[1]		Hypertension aggravated		Flushing, vasculitis, pulmonary embolism
Respiratory, thoracic, and mediastinal disorders				
	Pharyngitis, rhinitis, cough, dyspnoea[1]			Bronchospasm
Gastrointestinal disorders				
	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting[1]dysphagia[1]	Constipation, eructation, gastritis, stomatitis, aggravation of gastrointestinal inflammation	Duodenal, gastric, oesophageal, intestinal, and colonic ulceration; intestinal perforation; oesophagitis, melaena; pancreatitis	Nausea, gastrointestinal haemorrhage, colitis/colitis aggravated
Hepatobiliary disorders				
		Abnormal hepatic function, increased SGOT and SGPT	Elevation of hepatic enzymes	Hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis (some with fatal outcome), liver necrosis, hepatitis jaundice
Skin and subcutaneous tissue disorders				

	Rash, pruritus	Urticaria	Alopecia, photosensitivity	Ecchymosis, bullous eruption, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome), angioedema, acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				
		Leg cramps		Arthralgia, myositis
Renal and urinary disorders				
		Increased creatinine, BUN increased		Acute renal failure, interstitial nephritis, hyponatraemia
Reproductive system and breast disorders				
				Menstrual disorder NOS
General disorders and administrative site conditions				
	Flu-like symptoms, peripheral oedema/ fluid retention			Chest pain

[1] Adverse drug reactions that occurred in polyp prevention trials, representing subjects treated with celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials). The adverse drug reactions listed above for the polyp prevention trials are only those that have been previously recognized in the post-marketing surveillance experience, or have occurred more frequently than in the arthritis trials.

[2] Furthermore, the following *previously unknown* adverse reactions occurred in polyp prevention trials, representing subjects treated with celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials):
Common: angina pectoris, irritable bowel syndrome, nephrolithiasis, blood creatinine increased, benign prostatic hyperplasia, weight increased. **Uncommon:** helicobacter infection, herpes zoster, erysipelas, bronchopneumonia, labyrinthitis, gingival infection, lipoma, vitreous floaters, conjunctival haemorrhage, deep vein thrombosis, dysphonia, haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, allergic dermatitis, ganglion, nocturia, vaginal haemorrhage, breast tenderness, lower limb fracture, blood sodium increased.

[3] Adverse drug reactions spontaneously reported to the safety surveillance database over a period in which an estimated >70 million patients were treated with celecoxib (various doses, durations, and indications). As a result, the frequencies of these adverse drug reactions cannot be reliably determined. Adverse drug reactions listed for the post-marketing population are only those that are not already listed for the arthritis trials or the polyp prevention trials.

In final data (adjudicated) from the APC and PreSAP trials in patients treated with celecoxib 400 mg daily for up to 3 years (pooled data from both trials; see Section 5.1 for results from individual trials), the excess rate over placebo for myocardial infarction was 7.6 events per 1000 patients (uncommon) and there was no excess rate for stroke (types not differentiated) over placebo.

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.