VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Rheumatoid arthritis (RA) is an inflammatory disease. It largely affects synovial joints, which are lined with a specialised tissue called synovium. RA typically affects the small joints of the hands and the feet, and usually both sides equally and symmetrically, although any synovial joint can be affected. It is a systemic disease and so can affect the whole body, including the heart, lungs and eyes[1].There are approximately 400,000 people with RA in the UK. The

incidence of the condition is low, with around 1.5 men and 3.6 women developing RA per 10,000 people per year. This translates into approximately 12,000 people developing RA per year in the UK. The overall occurrence of RA is two to four times greater in women than men. The peak age of incidence in the UK for both genders is the 70s, but people of all ages can develop the disease1. Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. RA affects all populations, though it is much more prevalent in some groups (eg, 5-6% in some Native American groups) and much less prevalent in others (eg, black persons from the Caribbean region). Outcome in RA is compromised when diagnosis and treatment are delayed. The clinical course of RA is generally one of exacerbations and remissions. Approximately 40% of patients with this disease become disabled after 10 years, but outcomes are highly variable. Some patients experience a relatively self-limited disease, whereas others have a chronic progressive illness.[2].

Juvenile rheumatoid arthritis (JRA) is a form of arthritis in children ages 16 or younger that causes inflammation and stiffness of joints for more than six weeks. Unlike adult rheumatoid arthritis, which is chronic and lasts a lifetime, children often outgrow juvenile rheumatoid arthritis. However, the disease can affect bone development in the growing child[3]. Worldwide, JIA appears to occur more frequently in certain populations (eg, indigenous peoples) from such disparate areas as British Columbia and Norway. A study in Sweden found the prevalence of JIA there to be similar to that in Minnesota, approximately 85 cases per 100,000 population, with an incidence of 11 cases per 100,000 populations. A study from Germany found a prevalence rate of 20 cases per 100,000 populations, with an incidence rate of 3.5 cases per 100,000 population. Estimates from Norway include a prevalence rate of 148 cases per 100,000 population with an incidence rate of 22 cases per 100,000 population. The incidence of JIA in Japan has been reported to be low. Disease-associated mortality for JIA is difficult to quantify, but it is estimated to be less than 1% in Europe and less than 0.5% in North America. Most deaths associated with JIA in Europe are related to amyloidosis, and most in the United States are related to infections.[4].

Ankylosing spondylitis (AS), a spondyloarthropathy, is a chronic, multisystem inflammatory disorder involving primarily the sacroiliac (SI) joints and the axial skeleton. The outcome in patients with a spondyloarthropathy, including AS, is generally good compared with that in patients with a disease such as rheumatoid arthritis. AS is the most common of the classic spondyloarthropathies. Prevalence varies with the prevalence of the HLA-B27 gene in a given population, which increases with distance from the equator. In general, AS is more common in whites than in nonwhites. It occurs in 0.1-1% of the general population, with the highest prevalence in northern European countries and the lowest in sub-Saharan Africa. Approximately 1-2% of all people who are positive for HLA-B27 develop AS. This increases to 15-20% if they have a first-degree relative with HLA-B27 positive AS[5]. The estimated prevalence of ankylosing spondylitis in England is 0.14%, equivalent to approximately 74,000 people.[6].

[1]The management of rheumatoid arthritis in adults. National institute for Health and Care Excellence, August 2013

[2]http://emedicine.medscape.com/article/331715

[3]http://www.stanfordchildrens.org/en/topic/default?id=juvenile-rheumatoid-arthritis-90-P01722.

[4]http://emedicine.medscape.com/article/1007276-treatment

[5]Lawrence H Brent. Ankylosing Spondylitis and Undifferentiated Spondyloarthropathy. http://emedicine.medscape.com/article/332945-overview#a0156. 04 June 2013

[6]Apremilast for ankylosing spondylitis. Horizon Scanning Centre, November 2013

Osteoarthritis refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. It is the most common form of arthritis, and one of the leading causes of pain and disability worldwide. The most commonly affected peripheral joints are the knees, hips and small hand joints. Pain, reduced function and effects on a person's ability to carry out their day-to-day activities can be important consequences of osteoarthritis[7].

A heterogeneous group of inflammatory rheumatic diseases with predominant involvement of axial and peripheral joints and enthesitis (inflammation at the site of insertion of tendons and ligaments to bone). They also share other features such as anterior uveitis and bowel lesions similar to those found in Crohn's disease. Symptoms within the specific causes can overlap and may progress from one to another. There is a high incidence of HLA-B27 but negative rheumatoid factor tests[8]. Some of these seronegative arthritic conditions include psoriatic arthritis, Reiter's syndrome, enteropathic arthritis, reactive arthritis, ankylosing spondylitis, undifferentiated seronegative arthritic, Whipple's disease, arthritis associated with pustular acne, post-intestinal bypass arthritis, and several forms of HIV associated arthritis.[9].

An entire array of painful and sometimes disabling musculoskeletal syndromes exist that are not articular in origin but arise from tendons and bursae. These conditions are referred to by various names, in addition to tendinitis and bursitis, including the terms nonarticular rheumatism, soft tissue diseases, regional rheumatic pain syndromes, overuse syndromes, and repetitive use syndromes. These entities are often ignored, misdiagnosed as arthritis, or attributed to the aging process; awareness of the existence of these conditions and knowledge of basic musculoskeletal anatomy are the fundamental requirements for diagnosis[10].

Dysmenorrhea refers to the symptom of painful menstruation. It can be divided into 2 broad categories: primary (occurring in the absence of pelvic pathology) and secondary (resulting from identifiable organic diseases). Current evidence suggests that the pathogenesis of primary dysmenorrhea is due to prostaglandin F2α (PGF2α), a potent myometrial stimulant and vasoconstrictor, in the secretory endometrium. The response to prostaglandin inhibitors in patients with dysmenorrhea supports the assertion that dysmenorrhea is prostaglandin- mediated. Substantial evidence attributes dysmenorrhea to prolonged uterine contractions and decreased blood flow to the myometrium[11].

Fever is the temporary increase in the body's temperature in response to some disease or illness. Fever is an important part of the body's defense against infection. Most bacteria and viruses that cause infections in people thrive best at 98.6 °F. Many infants and children develop high fevers with minor viral illnesses. Although a fever signals that a battle might be going on in the body, the fever is fighting for the person, not against. Brain damage from a fever generally will not occur unless the fever is over 107.6 °F (42 °C). Untreated fevers caused by infection will seldom go over 105 °F unless the child is overdressed or trapped in a hot place. Unexplained fevers that continue for days or weeks are called fevers of undetermined origin (FUO) [12].

[7]Osteoarthritis. Care and management in adults. NICE clinical guideline 177, February 2014.
[8]http://www.natural-arthritis-pain-relief.org/seronegative-arthritis.html
[9]http://www.patient.co.uk/doctor/seronegative-arthropathies.
[10]https://www.inkling.com/read/cecil-textbook-of-medicine-goldman-schafer-24th/chapter-271/bursitis-tendinitis-and-other
[11.] http://emedicine.medscape.com/article/253812-treatment.
[12.] http://www.nytimes.com/health/guides/symptoms/fever/overview.html.

Gout is the most common inflammatory arthritis in men and in older women. It is closely associated with hyperuricemia and is characterized by the formation and reversible deposition of monosodium urate (MSU) crystals in joints and extra-articular tissues. Recent epidemiological studies have reported a rising prevalence and incidence of gout worldwide over the last two decades, especially in industrialized countries. Risk factors for hyperuricemia, such as obesity, hypertension, extensive use of diuretics and alcohol intake,
may in part explain this increasing trend.[13] The prevalence of gout appears to be rising in certain populations. A multicenter study conducted in the UK in 1991 found that the prevalence of gout had increased threefold compared with estimates from the 1970s. In a 1999 examination of gout epidemiology from the UK General Practice Research Database, gout prevalence was found to be approximately 2% among men and about 1% among men and women combined. Prevalence was highest among those aged 75–84 years; among the men
gout incidence approached 8%. Gout prevalence varies substantially by geographic region.[14]
Research using the UK primary care database reported the incidence of gout per 1,000 person- years to be 2.68 (4.42 in men and 1.32 in women) for the years 2000-2007. The prevalence increased with age. Asian populations and people of the Pacific Islands have a much higher prevalence and more severe disease. The male to female ratio is 9:1. The prevalence increases in women after the menopause although this is partly reduced by hormone replacement
therapy.[15]

VI.2.2 Summary of treatment benefits

Naproxen Aurobindo/Actavis film-coated tablets, gastro-resistant tablets and tablets are indicated as follows:

Naproxen 250mg and 500mg tabletten (National-Netherlands Aurobindo Pharma B.V)

- Rheumatoid arthritis, osteoarthritis and other inflammatory disorders of the musculoskeletal system.
- Pain and swelling after surgery, orthopedic operations and tooth extraction.
- Acute attacks of arthritis urica.
- Juvenile chronic arthritis.
- Symptomatic treatment of primary dysmenorrhea.
- Use as an antipyretic.
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Naproxennatrium Aurobindo 550 mg, filmomhulde tabletten (National-Netherlands Aurobindo Pharma B.V)

Rheumatic pain
Myalgia
Spit.

Naproxen Tablets BP 250mg and 500mg (National-United Kingdom)

Naproxen is used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhoea and acute gout.

Naproxen Actavis EC 250 &500 mg, maagsapresistente tabletten

Rheumatoid arthritis and osteoarthritis. Juvenile chronic arthritis in patients 18 years and older. Due to the delayed onset of the absorption is not EC Naproxen tablets suitable for use in situations where rapid analgesia and antipyretic is desired. Therefore, it is only allowed for indications that require chronic administration.

Naproxen Actavis 250 mg & 500mg, tabletten

[13] . Ciancio et al.,. Epidemiology of gout and chondrocalcinosis. Reumatismo, 2011; 63 (4): 207-220. [14] Kenneth G Saag et al.,. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Research & Therapy* 2006, **8(Suppl 1):**S2
[15] http://www.patient.co.uk/doctor/gout-pro

Naproxen tablets, tablets may be applied in rheumatoid arthritis, juvenile chronic arthritis, ankylosing spondylitis, degenerative joint disease, and other inflammatory disorders of the musculoskeletal system. Pain and swelling after surgery, orthopedic operations and tooth extraction.
Acute gout attack. Primary dysmenorrhea and fever

No additional studies were conducted as naproxen Aurobindo/Actavis is a generic medicine that is given orally and contains the same active substance as the reference medicine.

Because naproxen Aurobindo/Actavis is a generic, its beneficial treatment effects are taken as being the same as the reference medicines.

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns relating to treatment benefits that the MAH is aware of.

VI.2.4 Summary of safety concernsImportant identified risks

Risk	What is known	Preventability
Use in renal/hepatic impairment patients	The elderly and patients with hepatic impairment The lowest possible dose should be used. Naproxen is contraindicated in severe renal impairment In some patients, especially in patients where renal blood flow is compromised, such as depletion of the extracellular volume, liver cirrhosis, sodium restriction, heart failure and pre-existing renal disease, renal function should be monitored before and during therapy with naproxen. In some elderly impaired renal function can be expected, as well as patients taking diuretics, may fall into this category. A dose reduction should be considered to prevent the possibility of excessive accumulation of naproxen metabolites in these patients. In patients with renal insufficiency naproxen is administered with caution, especially if it is a long-term treatment. It should also be ensured adequate diuresis. In the case of a decreased renal perfusion, the renal function should be monitored before and during treatment with naproxen .	Physician supervision and care Dose adjustment

Precipitation of bronchospasm in patients suffering from or with a previous history of, bronchial asthma or allergic disease	Caution is required if administered to patients suffering from or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients Hypersensitivity reactions have been reported following treatment with NSAIDs in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).	Physician supervision and care
Long-term effects	In patients with renal insufficiency naproxen should be administered with caution, especially if it is a long-term treatment. Patients with uncontrolled hypertension, uncontrolled, congestive heart failure, ischemic heart disease, peripheral arterial disease, and / or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before long-term treatment is initiated in patients with risk factors for cardiovascular disease (eg hypertension, hyperlipidaemia, diabetes mellitus, and smoking).	Physician supervision and care
Gastrointestinal bleeding, ulceration and perforation	Naproxen may in principle not be administered to patients with ulceration of the gastrointestinal tract,	Naproxen must be discontinued immediately and

Risk	What is known	Preventability
	gastritis or congestive stiva atrophica gastritis, gastrointestinal bleeding or other bleeding such as cerebrovascular bleeding, the previous history of gastrointestinal bleeding or perforation caused by NSAID use, active or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding). Patients on concomitant naproxen and coumarin derivatives or heparin have an increased risk of bleeding. The risk of the occurrence of gastroduodenal ulcers or bleeding increases with the duration of the use of naproxen and higher dosage. This risk is not limited to a specific patient population, but the elderly and debilitated persons show less tolerance for gastro-intestinal ulcerations or bleeding than others. The most fatal gastrointestinal effects were attributed to prostaglandine synthesis inhibitors agents arrived at this population The elderly have more frequent side effects of NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms of severe or likely to occur gastrointestinal side effects The risk of GI bleeding, ulceration or perforation is higher at higher doses, a previous history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (eg misoprostol or proton pump inhibitors) should be considered	appropriate medical therapy instituted. Avoiod co-adminstration of naproxen with coumarin derivatives or heparin, corticosteroids and aspirin

Risk	What is known	Preventability
	for these patients and also in patients who require low dose aspirin, or other drugs likely to increase gastrointestinal risk Patients with a history of gastro-intestinal toxicity, especially the elderly, have had to report any unusual abdominal symptoms (especially gastrointestinal bleeding), especially at the beginning of the treatment. Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin- reuptake inhibitors and agents that counteract platelet aggregation such as aspirin. When necessary to gastrointestinal or ulceration occurs in patients receiving naproxen, stopped the treatment immediately. Gastrointestinal disorders Common (1≥ / 1,000, <1/100): bleeding from the gastrointestinal tract, peptic ulcers Rare (1≥ / 10,000 to <1 / 1,000): Perforation of the gastrointestinal tract, non-peptic ulcers	
Decreases platelet aggregation and prolongs bleeding time	Naproxen decreases platelet aggregation and prolongs bleeding time Naproxen can increase the effects of oral anticoagulants and heparin (increasing the risk of bleeding as a result of inhibition of platelet aggregation. Account should be taken of the opportunity to strengthen the effects of sulfonylureas (oral agents) by displacement of the plasma protein. Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses Platelet aggregation inhibitors and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding	Naproxen must be discontinued immediately and appropriate medical therapy instituted. Avoiod co-adminstration of naproxen with oral anticoagulants and heparin.

Risk	What is known	Preventability
	Blood and lymphatic system disorders Common (1≥ / 100, <1/10): increased bleeding time.	
Renal effects (such as impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis and occasionally nephrotic syndrome)	As can also be present at other naproxen prostaglandine synthesis inhibitors increase the likelihood of a renal disorder, if it is co-administered with ACE-inhibitors. Prostaglandine synthesis inhibitors such as naproxen can cause an increased nephrotoxicity of ciclosporin by their effects on renal prostaglandins. Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis in the mother and the neonate, at the end of pregnancy Renal and urinary disorders: Rare (1≥ / 10,000 to <1 / 1,000) Pollakiuria, proteinuria, glomerulonephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, renal failure, hematuria, elevated serum creatinine, hyperkalemia.	Avoiod co-adminstration of naproxen with ACE-inhibitors and ciclosporin Physician supervision and care
Concomitant use with oral corticosteroid, anticoagulants such as warfarin or heparin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin	Anaphylactic (anaphylactoid) reactions may occur in patients with and without a history of hypersensitivity or in patients not previously exposed to aspirin, naproxen (sodium) and other NSAIDs. They can also occur in patients with angioedema, bronchospastic reactivity (eg asthma), rhinitis, and nasal polyps in history. Anaphylactoid reactions, like anaphylaxis, fatal. Combination therapy with protective agents (eg misoprostol or proton pump inhibitors) should be considered for these patients and also in patients who require low dose aspirin, or other drugs likely to increase gastrointestinal risk Patients taking anticoagulants should be carefully observed while taking naproxen.	Physician supervision and care Avoid concomitant use with oral corticosteroid, anticoagulants such as warfarin or heparin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin

Risk	What is known	Preventability
	Patients with addition of naproxen to coumarin derivatives or heparin have an increased risk of bleeding. Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors and agents that counteract platelet aggregation such as aspirin. Corticosteroids: increased risk of gastrointestinal ulceration or bleeding Anticoagulants: NSAIDs may enhance the effects of anticoagulants such as warfarin	
Anaphylactic (anaphylactoid) reactions	Naproxen should not be administered to patients after administration of aspirin or other non-steroidal anti-inflammatory (prostaglandine synthesis inhibitor). It may cause an allergic reaction such as asthma, rhinitis or urticaria. Severe anaphylactic reactions have been reported in these patients. Anaphylactic (anaphylactoid) reactions may occur in patients with and without a history of hypersensitivity or in patients not previously exposed to aspirin, naproxen (sodium) and other NSAIDs. They can also occur in patients with angioedema, bronchospastic reactivity (eg asthma), rhinitis, and nasal polyps in history. Anaphylactoid reactions, like anaphylaxis, may be fatal. Immune system disorders: Rare (1≥ / 10,000 to <1 / 1,000): Anaphylactic reaction	Naproxen must be discontinued immediately and appropriate medical therapy instituted. Avoiod co-adminstration of naproxen with aspirin Avoid use in patients with history of hypersensitivity reactions Physician supervision and care
Cardiovascular and cerebrovascular effects	Patients with a history of hypertension and / or mild to moderate congestive heart failure should receive appropriate monitoring and advice as fluid retention and edema have been reported in association with NSAID	Naproxen must be discontinued immediately and appropriate medical therapy instituted.

Risk	What is known	Preventability
	therapy. Data from clinical studies and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and long term use), may be associated with a small increased risk of thrombosis in the arteries (for example myocardial infarction or stroke). Epidemiological studies suggest that at low doses of naproxen (1000 mg per day) may be associated with a lower risk, some risk can not be excluded. Patients with uncontrolled hypertension, uncontrolled, congestive heart failure, ischemic heart disease, peripheral arterial disease, and / or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before long-term treatment is initiated in patients with risk factors for cardiovascular disease (eg hypertension, hyperlipidaemia, diabetes mellitus, and smoking). The absolute risk for cardiovascular malformation was increased from less than 1% to approximately 1.5% catalyst. It is believed that the risk increases with the dosage and the treatment duration. Cardiac disorders: Common (1≥ / 1,000,<1/100) Palpitations; Rare (1≥ / 10,000 to <1 / 1,000): Elevated blood pressure, heart failure	Physician supervision and care
Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal)	Hepatobiliary disorders: Rare (1≥ / 10,000 to <1 / 1,000) : Increase in transaminases or alkaline phosphatase, increased bilirubin, jaundice, hepatitis, with some cases with fatal outcome.	Naproxen must be discontinued immediately and appropriate medical therapy instituted. Physician supervision and care

Risk	What is known	Preventability
Aseptic meningitis	In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis Aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation	Physician supervision and care
Serious skin reactions (including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)	If the skin is tender, blisters or other symptoms occur, pointing to serious skin reactions treatment should be discontinued and the patient should be monitored closely. Serious skin reactions may be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, they have been reported very rarely in association with the use of NSAIDs	Naproxen must be discontinued immediately and appropriate medical therapy instituted. Physician supervision and care
Ocular effects including papillitis, retrobulbar optic neuritis and papilloedema	Studies have not shown changes in the eye attributable to naproxen administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema, have been reported in users of NSAIDs including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with naproxen-containing products should have an ophthalmological examination. Undesirable effects: Eye Disorders: Visual disturbances, corneal opacity, papillitis and papilloedema.	Naproxen must be discontinued immediately and appropriate medical therapy instituted. Physician supervision and care

Risk	What is known	Preventability
Impaired fertility in female	The use of naproxen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or undergoing investigation of infertility, the use of naproxen should be avoided There is some evidence that agents that inhibit cyclo-oxygenase / prostaglandin synthesis reduce female fertility by an effect on ovulation. This is reversible by discontinuation of treatment.	Physician supervision and care
Combination with other NSAIDs	Anaphylactic (anaphylactoid) reactions may occur in patients with and without a history of hypersensitivity or in patients not previously exposed to aspirin, naproxen (sodium) and other NSAIDs The use of naproxen with other NSAIDs, including selective COX-2 inhibitors should be avoided. The combination with other NSAIDs is contraindicated due to the toxicity of the combination therapy and the lack of evidence for a therapeutic benefit.	Naproxen must be discontinued immediately and appropriate medical therapy instituted. Combination with other NSAIDs is contraindicated
Congenital abnormalities	Inhibition of prostaglandin synthesis may affect pregnancy and / or the embryo / fetal development. Data from epidemiological studies suggest an increased risk of • miscarriage and of cardiac malformation and gastroschisis after use of prostaglandin synthesis inhibitors may occur in the early phase of pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% to approximately 1.5%. It is believed that the risk increases with the dosage of the treatment duration. Administration of a prostaglandin synthesis inhibitor in animals resulted in increased pre- and post- implantation loss and embryo-fetal lethality. In addition, an increased	Naproxen is contraindicated during the third trimester of pregnancy Physician supervision and care

Risk	What is known	Preventability
	incidence of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the period of organogenesis. During the first and second trimester of pregnancy naproxen should not used unless clearly necessary. When naproxen is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as short as possible and treatment is as short as possible. Use of prostaglandin synthesis inhibitors during the third trimester of pregnancy expose the fetus to: - Cardiopulmonary toxicity (with premature closure of the ducuts arteriosus and pulmonary hypertension); - Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; - Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; - Inhibition of the contraction of the uterus, resulting in a delayed or prolonged labor. Due to this, naproxen is contraindicated during the third trimester of pregnancy	
Use in breast feeding	**As per the UK-National SPC** In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. The use of naproxen should be avoided in patients who are breastfeeding.	Naproxen must be avoided in breastfeeding Physician supervision and care
Use in elderly patient	The lowest possible dose should be used and for the shortest possible duration. In some elderly patients impaired renal function can be expected, as	Dosage adjustment Physician supervision and care

Risk	What is known	Preventability
	well as patients taking diuretics, may fall into this category. A dose reduction should be considered to prevent the possibility of excessive accumulation of naproxen metabolites in these patients. Serious gastrointestinal adverse reactions may occur in patients taking prostaglandin synthesis inhibitors. The risk of the occurrence of gastroduodenal ulcers or bleeding increases with the duration of the use of naproxen. And dosage This risk is not limited to a specific patient population, but the elderly and debilitated persons show less tolerance for gastro-intestinal ulcerations or bleeding than others. The fatal gastrointestinal effects were attributed to prostaglandin synthesis inhibitors used in this population High doses are naproxen should not be administered to elderly patients as there are indications that blood level of naproxen is increased in these patients. The elderly have more frequent side effects of NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal The risk of GI bleeding, ulceration or perforation is higher at higher doses, a previous history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) and in the elderly. Patients with a history of gastro-intestinal toxicity, especially the elderly, have had to report any unusual abdominal symptoms (especially gastrointestinal bleeding), especially at the beginning of the treatment	The lowest effective dose should be used in the elderly and for the shortest possible duration.

Important potential risks

None

Missing information

None

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

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation

None

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
NA	NA	NA	NA

Major changes to the Risk Management Plan over time