VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Naproxen is used for the reduction of inflammation, pain, fever and stiffness caused by conditions including rheumatoid arthritis (including juvenile), Bekhterev's disease, migraine, dysmenorrhea and mild to moderate pain.

It is estimated that some of the causes of chronic disability is pain arised from conditions such as inflammation in joints (including rheumatoid arthritis), as well as back pain and spine problems. Chronic pain accounts for the highest percentage, about 35%, of the total chronic disability due to various chronic pain syndromes. Internationally, chronic pain prevalence estimates range from 10.1% to 55.2%. Pain such as musculoskeletal pain can affect the quality of life. Activity of daily living is impaired. Pain can cause mood changes and decreased involvement in activities.

In 2006, acute pain was a frequent "chief complaint" for adults who presented to emergency departments in USA, and pain severity was reported as moderate to severe by 45% of patients in the ED. Population experiencing acute pain tend to be higher than chronic pain. A study conducted in Spain indicates a prevalence of 78.6% among common population over six months.

Back pain and headaches were most prevalent. Chronic pain affects ~20% of the European population and is commoner in women, older people, and with relative deprivation.

VI.2.2 Summary of treatment benefits

Naproxen belongs to a group of medication known as NSAID and works by reversibly inhibiting COX enzymes within the body. It is the preferred NSAID for long-term use in people with a high risk of cardiovascular complications due to its relatively low risk of causing such complications. Naproxen has an intermediate risk of causing stomach ulcers as compared with other NSAIDs. It is commonly used for relief of a wide variety of pain, fever, swelling and stiffness.
As a pain reliever, fever reducing and anti-imflammatory drug, naproxen has been well studies in controlled clinical trials. The therapeutic efficacy of naproxen is kept during long-term treatment as well as the tolerability is well established and understood.

VI.2.3 Unknowns relating to treatment benefits

Naproxen has been on the market for over 40 years and its safety profile is well-established.

If taken during pregnancy it may result in harm. During breastfeeding naproxen passess through the breast milk and should be avoided if possible. Treatment of children under the age of 5 (five) years old is not well established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Gastrointestinal ulcers	Gastrointestinal ulceration or perforation, which can be fatal, has been reported with naproxen at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal bleeding, events. The risk of GI ulceration or perforation is higher with increasing doses and in patients with a history of ulcer.	Undesirable effects such as ulcer may be minimized by using the lowest effective dose for the shortest duration necessary to keep symptoms under control. Patients with history of ulcer should commence treatment on the lowest dose available. Combination therapy with protective agents which can prevent ulcer should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk. Patients with a history of gastrointestinal disease, particularly when elderly,

Risk	What is known	Preventability
		should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, anticoagulants such as selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin. When gastrointestinal ulceration occurs in patients receiving naproxen, the treatment should be withdrawn.
Liver failure	Naproxen is extensively metabolized in the liver and little is excreted unchanged. Any reduction in liver functionality is expected to reduce the excretion of naproxen, therefore the naproxen concentration in the blood will increase. Very rarely naproxen is known to impair liver function, damage liver, especially during long-term treatment, cause hepatic failure, acute hepatitis or jaundice.	In patients with mild to moderate hepatic impairment, treatment should be initiated as low a dose as possible given for the shortest duration necessary to control symptoms. Liver function and renal function should be monitored.
Renal failure	The administration of naproxen may cause a dose dependent reduction in prostaglandin (hormone-like lipid compounds secreted in the body) formation and result in renal failure. Similar to other naproxen like drugs, long-term administration of naproxen may result in renal cell damage and other renal changes at tissue level.	Undesirable effects such as renal failure may be minimized by using the lowest effective dose for the shortest duration necessary to keep symptoms under control. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be

Risk	What is known	Preventability
		monitored in patients with history of renal diseases. Renal toxicity has also been seen in patients in whom renal prostaglandins (a hormone-like lipid substance secreted in the kidney) have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an naproxen may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of naproxen therapy is usually followed by recovery to the pre-treatment state.
Heart failure	Epidemiological data suggest that use of naproxen, may be associated with a small increased risk of heart related events such as heart attack or stroke.	Undesirable effects such as heart failure may be minimized by using the lowest effective dose for the shortest duration necessary to keep symptoms under control. Naproxen should not be given to patients with conditions involving heart failure and therefore it is contraindicated in patients with heart failure.
Gastrointestinal bleeding	Gastrointestinal bleeding can be fatal and it has been reported with all drugs which belong to the same category as naproxen at	Undesirable effects such as gastrointestinal bleeding may be minimized by using

Risk	What is known	Preventability
	any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal bleeding, events. The risk of gastrointestinal ulceration or perforation or bleeding is higher with increasing naproxen doses, in patients with a history of ulcer or bleeding, particularly.	the lowest effective dose for the shortest duration necessary to keep symptoms under control. Patients with history of gastrointestinal bleeding should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk. Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. Caution should be 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 or anti-platelet agents such as aspirin. When GI bleeding or ulceration occurs in patients receiving naproxen, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of ulcerative colitis or Crohn's disease as these conditions may be exacerbated.
Use in pregnancy	Inhibition of (prostaglandin hormone-like compounds secreted in the body) synthesis	Pregnant women should be informed of the possible

Risk	What is known	Preventability
	may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of heart malformation and birth defect in stomach after the use of a prostaglandin synthesis inhibitor in early pregnancy. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the initial foetal development period.	complications to pregnancy which ould occur if treated with naproxen. Health care proffesionals should informe patients and avoid prescription during pregnancy.

Important potential risks

Risk	What is known	Preventability
Interaction with other medicines	Naproxen in combination with other treatments can increase the risk of adverse events. Particularly co-treatment with other NSAIDs is not recommended due to an increased cumulative risk of serious NSAID-related adverse events. Furthermore in combinations with certain medications it is possible to increase or decrease the effect of either treatment. Certain medications when given together with naproxen might result in increase risk of adverse events such as but not limited to: increase bleeding (incl. gastrointestinal bleeding) and acute renal failure)	Undesirable effects such as interaction with other medicinces can be minimised by using the lowest effective dose for the shortest duration necessary to keep symptoms under control. Both the healthcare professionals and patient should be aware of such potential interactions and inform their treating phycian of any ongoing treatments and any adverse events as soon as possible.

Missing information

Risk	What is known
Use in Children under the age of five.	There is not enough studies performed for young children under the age of five. Theoretically the same profile for older children will apply with similar possible adverse events however more controlled clinical studies are required.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Naproxen Apofri can be found in the Naproxen Apofri's *European public assessment reports* (*EPAR*) page.

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan

Not applicable

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

Version No.	***Reason for change***	***Date of issuance***
2.0	Changes requested by assessors	
1.0	Original document (submitted in the application dossier).	01 Dec 2016