PROFESSIONAL INFORMATION

SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

Aleve® 220 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Naproxen sodium 220 mg (equivalent to 200 mg naproxen)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Aleve® is presented as a light blue, film coated oval shape tablet, each containing 220 mg naproxen sodium.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aleve® is indicated for the short-term management of headache, toothache, muscular ache, backache, pain of menstrual cramps (dysmenorrhoea), minor aches and pain associated with the common cold and fever.

4.2. Posology and method of administration

Adults:

- 1 tablet every eight to twelve hours while symptoms persist.
- With experience, some patients may find that an initial dose of 2 tablets followed by 1 tablet 12 hours later, if necessary, will give better relief.
- 3 tablets in 24 hours should not be exceeded unless directed to do so by a doctor.
- Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (See Section 4.4). Aleve® must not be taken for more

than ten days, unless under the direction of a doctor. If pain or fever persists or if symptoms change, a doctor should be consulted.

Elderly (65 and over):

- No more than 2 tablets per day, unless directed to do so by a doctor.

Children:

- Do not give this medicine to children under 12 years, except under the advice and supervision of a doctor.

Dose in Severe Renal, Hepatic or cardiac Impairment:

- In patients with severe, renal, hepatic and/ or cardiac impairment dose reduction may be necessary.

Method of administration

Each dose should be taken orally with a glass of water and can be taken fasting or with meals. Absorption may be delayed with meals.

4.3. Contraindications

- Known hypersensitivity to naproxen or any other ingredient in the medicine
- History of asthma, urticaria or allergic-type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).
- History of gastrointestinal bleeding or perforation related to previous NSAID therapy.
- Active, or a history of, recurrent peptic ulcer or haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure.
- Aleve® is contraindicated in pregnant or nursing mothers.

4.4. Special warnings and precautions for use

Pain of gastrointestinal origin is not an indication for Aleve®.

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General Warnings:

The use of Aleve® with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see gastrointestinal and cardiovascular risks below).

Precautions for Elderly Patients:

Although total plasma concentrations of naproxen are unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised and lower doses might be required. For the effects of reduced elimination in the elderly refer to the section – *Use in patients with impaired renal function.*

Use in patients with impaired renal function:

As naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and /or creatinine clearance is advised in these patients.

Certain patients, specifically those where renal blood flow is compromised, such as in extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure and pre-existing renal disease, should have renal function assessed before and during Aleve® therapy. Elderly patients in whom impaired renal function may be expected could also fall within this category. A reduction in daily dosage is recommended to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

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Gastrointestinal bleeding, ulceration and perforation:

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See section 4.3), and in the elderly. These patients 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 (See section 4.5).

Patients with a history of gastrointestinal toxicity, 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 (See section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving Aleve®, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (See section 4.8).

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Sodium/fluid retention in cardiovascular conditions and peripheral oedema:

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Cardiovascular and cerebrovascular effects:

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded. There are insufficient data regarding the effects of low dose Aleve® (220 mg – 660 mg daily) to draw firm conclusions on possible thrombotic risks.

Aleve® may attenuate acetylsalicylic acid's antiplatelet effect. Patients should talk to their doctor if they are on an acetylsalicylic acid regimen and plan to take Aleve®. (See section 4.5)

Skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Steven's-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (See section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy. Aleve® should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Anaphylactic (anaphylactoid) reactions:

Hypersensitivity reactions, including anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity on exposure to aspirin, other non-steroidal anti-inflammatory drugs or naproxen-containing products. They may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma), rhinitis, nasal polyps,

allergic disease, chronic respiratory disease or aspirin sensitivity. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching urticaria) to naproxen or other NSAIDs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Hepatic effects:

Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal), have been reported with Aleve® as with other non-steroidal anti-inflammatory drugs. Cross reactivity has been reported.

Precautions related to fertility:

There is some evidence that drugs which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Patients with medical history

Subjects with the following additional medical history should be under adequate and careful supervision of their doctor when taking Aleve®:

- Those taking any other analgesic
- Those taking steroids
- Those with coagulation disturbances or who take medicines that influence haemostasis
- Those on intensive diuretic therapy
- Those with severe renal, hepatic, or cardiac impairment

4.5. Interaction with other medicines

Cyclosporine:

Cyclosporine concentrations may increase, increasing the risk for nephrotoxicity.

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Lithium:

Lithium levels may increase, which could induce nausea, polydipsia, polyuria, tremor, confusion.

Methotrexate used at doses of 15 mg/week or more:

Elevated concentration of methotrexate, increasing the risk for toxicity to this substance.

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin:

Increased risk of ulcers and gastrointestinal bleeding. (See section 4.4).

Low-dose aspirin:

Aleve® may attenuate the irreversible platelet inhibition induced by acetylsalicylic acid.

Clinical pharmacodynamic data suggest that concurrent (same day) Aleve® usage for more than one day consecutively inhibits the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping Aleve® therapy. The clinical relevance of this interaction is not known. Treatment with Aleve® in patients with increased cardiovascular risk may limit the cardiovascular protection of acetylsalicylic Acid. (See section 4.4).

Anticoagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4). Anticoagulants and other drugs influencing haemostasis add to the risk of bleeding and require careful monitoring.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding (See section 4.4).

Corticosteroids:

Increased risk of gastro-intestinal ulceration or bleeding (See section 4.4).

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Diuretics and antihypertensive drugs including ACE Inhibitors:

The diuretic and antihypertensive efficacy, particularly in patients with pre-existing nephropathy, may be reduced.

During short term use of Aleve® interactions of clinical significance do not seem to be relevant for the following medications:

- Antacids
- Antidiabetic agents
- Hydantoins
- Probenecid
- Zidovudine

Drug – Food Interaction

The absorption of Aleve® may be delayed with a meal.

Interference with Laboratory Testing

Aleve® has been claimed to interfere with the urinary analyses of 17-ketogenic steroids and 5-hydroxy indoleacetic acid (5 HIAA).

4.6. Fertility, pregnancy and lactation

Pregnancy

As with other drugs of this type, Aleve® produces a delay in parturition in animals and also affects the human foetal cardiovascular system (closure of the ductus arteriosus). Therefore, Aleve® should not be used unless clearly needed and directed to do so by a doctor. The use of Aleve® in pregnancy requires cautious balancing of the possible benefits against potential risk to the mother and foetus, especially during the first and third trimester.

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Breastfeeding

Naproxen has been found in the milk of lactating mothers. The use of Aleve® should therefore be avoided in women who are breast-feeding.

4.7. Effects on the ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, undesirable effects such as drowsiness, dizziness, vertigo, insomnia have been observed with the use of Aleve®. Patients should be cautioned to see how they react before driving or operating machinery.

4.8. Undesirable effects

Cardiac disorders

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (See section 4.4).

Gastrointestinal disorders

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur. (See section 4.4).

Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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Skin and subcutaneous tissue disorders

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

Aleve® causes transient, dose-dependent modestly increased bleeding times. However, these values often do not exceed the upper limit of the reference range.

Tabulation of SIDE EFFECTS

The following adverse drug reactions have been observed for Aleve®, including those with prescription dosing.

System organ class	Frequency	Effects
Immune System disorders	Very rare < 0.01% and isolated reports	Anaphylaxis/ anaphylactoid reactions including shock with fatal outcome
Blood and the lymphatic system disorders	Very rare < 0.01% and isolated reports	haematopoietic disturbances (leucopoenia, thrombocytopenia, agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia)
Psychiatric disorders	Very rare < 0.01% and isolated reports	psychiatric disorders, depression, dream abnormalities, inability to concentrate
Nervous system disorders	Common = 1% - < 10%	dizziness, headache, light-headedness
	Uncommon = 0.1 % - < 1 %	drowsiness, insomnia somnolence
	Very rare < 0.01% and isolated reports	aseptic meningitis, cognitive dysfunction, convulsions
Eye disorders	Very rare < 0.01% and isolated reports	visual disturbance, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema

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System organ class	Frequency	Effects
Ear & labyrinth disorders	Uncommon = 0.1 % - < 1 %	Vertigo
	Very rare < 0.01% and isolated reports	hearing impairment, tinnitus, hearing disturbances
Cardiac disorders	Very rare < 0.01% and isolated reports	congestive heart failure, hypertension, pulmonary oedema, palpitations
Vascular disorders	Very rare < 0.01% and isolated reports	vasculitis
Respiratory, Thoracic and Mediastinal disorders	Very rare < 0.01% and isolated reports	dyspnoea, asthma, eosinophilic pneumonitis,
Gastro-intestinal disorders	Common = 1% - < 10%	dyspepsia, nausea, heartburn, abdominal pain
	Uncommon = 0.1 % - < 1 %	diarrhoea, constipation, vomiting
	Rare = 0.01% - < 0.1%	peptic ulcers without or with bleeding or perforation, gastrointestinal bleeding, hematemesis, melena
	Very rare < 0.01% and isolated reports	pancreatitis, colitis, aphthous ulcers, stomatitis, esophagitis, intestinal ulcerations
Hepatobiliary disorders	Very rare < 0.01% and isolated reports	hepatitis, (including fatal cases), jaundice, icterus
	Uncommon = 0.1 % - < 1 %	exanthema (rash), pruritus, urticaria

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System organ class	Frequency	Effects
Skin & Subcutaneous Tissue disorders	Rare = 0.01% - < 0.1%	angioneurotic oedema
	Very rare < 0.01% and isolated reports	alopecia (usually reversible), photosensitivity, porphyria, exudative erythema multiforme, bullous reactions including Steven's-Johnson syndrome and toxic epidermal necrolysis, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, Systemic Lupus Erythematosus, photosensitivity reactions including porphyria cutanea tarda ("pseudoporphyria") or epidermolysis bullosa, ecchymoses, purpura, sweating
Renal & Urinary disorders	Rare = 0.01% - < 0.1%	renal impairment
	Very rare < 0.01% and isolated reports	interstitial nephritis, renal papillary necrosis, nephrotic syndrome, renal failure, renal disease haematuria, proteinuria
Congenital	Very rare < 0.01% and isolated reports	Closure of ductus arteriosus
Reproductive system and breast disorders	Very rare < 0.01% and isolated reports	female: infertility

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System organ class	Frequency	Effects
General disorders	Rare = 0.01% - < 0.1%	peripheral oedema, particular in patients with hypertension or kidney failure, pyrexia (including chills and fever)
	Very rare < 0.01% and isolated reports	oedema, thirst, malaise
Investigations	Very rare < 0.01% and isolated reports	raised serum creatinine, abnormal liver function test, hyperkalemia

Reporting of suspected adverse reactions

Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form",** found under SAHPRA's publications: Https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

Significant overdosage of the drug may be characterised by dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea and vomiting, transient alterations in liver function, hypoprothrombinaemia, renal dysfunction, metabolic acidosis, apnea, or disorientation. Because Aleve® tablets may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear these were naproxen related or not. Some cases with acute, reversible renal failure have been described. It is not known what dose of the drug would be life threatening.

Should a patient ingest a large quantity of Aleve® tablets the stomach may be emptied and usual supportive measures like administration of activated charcoal employed. Haemodialysis does not

decrease the plasma concentration of naproxen because of the high degree of its protein binding. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A / 2.7 Antipyretic or antipyretic and anti-inflammatory analgesic

Musculo-skeletal system, anti-inflammatory and anti-rheumatic products, non-steroids, propionic acid derivative, ATC code: MO1A E02.

Naproxen belongs to the group of (non-aspirin) non-steroidal anti-inflammatory drugs which through reversible inhibition of the prostaglandin synthesis exert analgesic, antipyretic and anti-inflammatory functions. Naproxen is a non-selective COX inhibitor; it works by inhibiting both the COX-1 and COX-2 enzymes. It inhibits the formation of COX-1 dependent thromboxane synthase, A2 (TXA2), which reduces platelet aggregation, and the COX-2 dependent prostacyclin, (PGI2), which is an important vasodilatory mediator. Naproxen provides pain relief, lowers the fever and reduces the inflammatory response.

5.2. Pharmacokinetic properties

Naproxen sodium promptly dissolves in the gastric medium and is rapidly and completely absorbed from the gastrointestinal tract. Significant naproxen plasma levels and onset of pain relief can be obtained within 20 minutes of intake and peak levels (C_{max}) are attained in about 1 hour (t_{max}). Following absorption, more than 99% is bound to serum albumin. The volume of distribution is app. 0.1 l/kg and the elimination half-life ($t_{½}$) app. 14 hours. Naproxen is, after hepatic metabolism, primarily (≥ 95%) excreted through the kidneys. The pharmacokinetic data show linearity in the recommended dosage. Patients with severe hepatic impairment may have higher free naproxen

levels. In severe renal insufficiency naproxen, elimination is impaired, but no significant accumulation has been observed at the recommended dosage.

5.3. Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate, microcrystalline cellulose, opadry blue YS-1-42I5 CI: 73015, povidone K-30, purified water, talc.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 25 °C. Protect from light. Keep out of reach of children.

6.5. Nature and contents of container

Aleve® is available in blister packs of 12 tablets.

7. MANUFCATURER

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8. DATE OF REVISION OF TEXT

21 December 2020