PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S1

PROPRIETARY NAME AND DOSAGE FORM:

Aleve® Tablets

COMPOSITION:

Each tablet contains naproxen sodium 220 mg (equivalent to 200 mg naproxen)

CATEGORY AND CLASS:

A / 2.7 Antipyretic or antipyretic and anti-inflammatory analgesic

PHARMACOLOGICAL ACTION:

Aleve® (naproxen sodium) has analgesic, anti-inflammatory and anti-pyretic properties. It inhibits prostaglandin synthetase.

Aleve® is fully absorbed when administered orally. Peak plasma concentrations occur in 1 to 2 hours after administration.

The half-life of naproxen in plasma is about 13 hours.

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.

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CONTRA-INDICATIONS:

Aleve® is contra-indicated in pregnant or nursing mothers.

Aleve® is not recommended for patients who have previously exhibited allergy to naproxen or naproxen sodium, aspirin or other non-steroidal anti-inflammatory drugs.

WARNINGS AND SPECIAL PRECAUTIONS:

Asthma sufferers should only take Aleve® after consulting their doctor. Caution is advised in patients with coagulation disorders or who are receiving medicine therapy for coagulation disorders. Aleve® should not be taken with other anti-inflammatory medicines (including other naproxen or naproxen sodium products) except under the direction of a doctor.

Aleve® is indicated only for short-term use (10 consecutive days maximum) and should not be taken for longer periods unless directed by a doctor. Patients are advised to seek medical advice if their pain and fever persists or worsens, or if new or unusual symptoms develop while taking the medicine. They should also consult their doctor or pharmacist if they are taking any other medication regularly before taking Aleve®, or if they experience more than mild heartburn, dyspepsia or gastric discomfort with use of the product, or if such mild symptoms persist.

Aleve® should not be given to patients with cardiovascular disease, bleeding disorders, peptic ulceration or a history of such ulceration.

Aleve® is not recommended for patients who have previously exhibited allergy to naproxen or naproxen sodium, aspirin or other non-steroidal anti-inflammatory medicines.

Special Precautions:

Episodes of gastro-intestinal bleeding have been reported in patients on Aleve® therapy. Aleve® should be given under close supervision to patients with a history of gastro-intestinal disease.

Serious gastro-intestinal adverse reactions, including haemorrhage and perforation, can occur at any time in patients on therapy with non-steroidal anti-inflammatory agents. The risk of their

occurrence appears to increase linearly with the duration of use and is probably associated with the use of higher doses of these medicines. Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, elderly and debilitated patients tolerate gastro-intestinal ulceration or bleeding less well than others; most serious gastro-intestinal events associated with non-steroidal anti-inflammatory agents occurred in this patient population.

The antipyretic and anti-inflammatory activities of Aleve® may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Sporadic abnormalities in laboratory tests (e.g. liver function tests) have occurred in patients on Aleve® therapy.

Aleve® decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined. Patients who have coagulation disorders, or who are receiving medicine therapy that interferes with haemostasis, should be carefully observed if they are taking Aleve®. Patients on full anticoagulant therapy (e.g. heparin or warfarin) may be at an increased risk of bleeding if given Aleve® concurrently.

Peripheral oedema has been observed in a few patients receiving Aleve®. It is possible that patients with questionable or compromised cardiac function may be at greater risk when taking Aleve®.

<u>Use in patients with impaired renal function:</u>

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.

Use in patients with impaired liver function:

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen but the plasma concentration of unbound naproxen is increased. Caution is advised and lower doses might be required when using Aleve® in patients with hepatic diseases.

Use in the elderly:

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

Interactions with other medication:

Due to the high plasma protein binding of Aleve®, patients simultaneously receiving hydantoins, anti-coagulants or other highly protein-bound medicines should be observed for signs of potentiation or overdosage of these medicines. No interactions have been observed between Aleve® and warfarin or tolbutamide. Caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Aleve® can reduce the anti-hypertensive effect of propranolol and possibly other beta-blockers and may increase the risk of renal impairment associated with the use of ACE-inhibitors.

The natriuretic effect of furosemide has been reported to be inhibited by Aleve®.

Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

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Probenecid given concurrently increases Aleve® plasma levels and extends its plasma half-life considerably.

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, probably by reducing the tubular secretion of methotrexate.

It is suggested that Aleve® therapy be temporarily discontinued forty eight hours before adrenal function tests are performed because Aleve® may artificially interfere with some tests for 17-ketogenic steroids. Similarly, Aleve® may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

DOSAGE AND DIRECTION FOR USE:

Each dose should be swallowed with water.

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.

Elderly (65 and over):

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

Children:

- Do not give this drug to children under 16 years, except under the advice and supervision of a doctor.

SIDE EFFECTS:

Gastro-intestinal: The more frequent reactions are nausea, vomiting, abdominal discomfort, constipation and epigastric distress. More serious reactions which may occur are gastro-

intestinal bleeding and peptic ulceration (sometimes with haemorrhage and perforation) and colitis.

Dermatological/Allergy: Skin rashes, urticaria, angio-oedema. Anaphylactic reactions to naproxen and naproxen sodium formulations, eosinophilic pneumonitis, alopecia, erythema multiforme, Stevens Johnson syndrome, epidermal necrolysis and photosensitivity reactions including less frequent cases in which the skin resembles porphyria cutanea tarda ('pseudoporphyria') or epidermolysis bullosa may occur.

Renal: Including but not limited to glomerular nephritis, intestinal nephritis, nephrotic syndrome, haematuria, papillary necrosis, renal failure.

Central nervous system: Convulsions, headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

Haematological: Thrombocytopenia, granulocytopenia including agranulocytosis, aplastic anaemia and haemolytic anaemia may occur.

Other: Tinnitus, visual disturbances, hearing impairment, vertigo and mild peripheral oedema. Anaphylactic reactions to naproxen and naproxen sodium formulations have been reported in patients with, or without, a history of previous allergic reactions to NSAIDs. Jaundice, fatal hepatitis, eosinophilic pneumonitis, vasculitis, aseptic meningitis, hyperkalaemia and ulcerative stomatitis have been reported less frequently.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENTS:

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea and vomiting.

A few patients have experienced convulsions but it is not clear these were naproxen related or not. It is not known what dose of the drug would be life threatening.

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Should a patient ingest a large quantity of Aleve® accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. The prompt administration of activated charcoal in adequate amounts tends to reduce markedly the absorption of the drug.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

IDENTIFICATION:

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

PRESENTATION:

Aleve® is available in blister packs of 12 tablets.

STORAGE INSTRUCTIONS:

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

REGISTRATION NUMBER:

31 / 2.7 / 0145

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd

27 Wrench Road

Isando, 1600

South Africa

PROFESSIONAL INFORMATION

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date on the registration certificate of the medicine: 19 March 1998

Date of the most recently revised package insert as approved by Council: 17 January 1997

Manufactured and packed by Bayer Bitterfeld GmbH, Germany.