NDAC Briefing Document: Review of the Safety and Efficacy of OTC Naproxen Sodium

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Glossary of Abbreviations and Terms

ADERS	Adverse Events Reporting System
ADR	Adverse Drug Reaction
APAP	Acetaminophen
CHPA	Consumer Healthcare Products Association
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal
IBU	Ibuprofen
NAP	Naproxen Sodium
NDA	New Drug Application
NDAC	Non-prescription Drug Advisory Committee
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PDR	Physicians Desk Reference
PK/PD	Pharmacokinetic/Pharmacodynamic
PRN	As needed
RX	Prescription strength
TESS	American Association of Poison Control Centers' Toxic Exposure Surveillance System
WHO	World Health Organization

1 EXECUTIVE SUMMARY

The Bayer Corporation has extensive experience with over-the-counter (OTC) analgesics, and extensive marketplace experience with their safety and efficacy. It is Bayer's position that each of the currently approved OTC analgesics (naproxen sodium, aspirin, acetaminophen, ibuprofen, and ketoprofen) used according to package labeling is safe and effective for treatment of mild to moderate pain and reduction of fever.

Bayer is committed to do everything possible to ensure that its products are used safely to the benefit of the consumer. Accordingly, Bayer supports efforts by the FDA to identify patient risk factors that may be associated with use of OTC non-steroidal anti-inflammatory drugs and consideration of measures that could be taken to reduce the risk of occurrence or to decrease morbidity if an event should occur. Bayer also supports measures to encourage consumers to use these and all OTC products in accordance with approved labeling. These measures could include a variety of means, including changes to class labeling, intended to better educate and inform the consumer. Since each drug class represented among the approved OTC analgesic drugs has its characteristic pharmacology and adverse event profile, Bayer believes that changes to labeling that are identical across all OTC analgesics are scientifically inaccurate and do not serve the public interest.

The Bayer product line includes naproxen sodium (Aleve®). Naproxen sodium has been available in the United States since 1980. As a prescription drug naproxen sodium was the subject of a New Drug Application (NDA), that established its safety and efficacy based on a rigorous pre-marketing review of pre-clinical and clinical data. After 14 years of prescription use, naproxen sodium was approved by FDA for OTC use under the trade name Aleve® in 1994. Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID) used for a variety of pain disorders.

Each class of approved OTC analgesic drugs has its unique pharmacology and a characteristic adverse event profile. The adverse event profiles of the NSAIDs are well known. The majority of the available literature addresses NSAID adverse events observed at prescription doses. NSAIDs are known to have effects on the gastrointestinal, hepatic, and renal systems. The potential for serious gastrointestinal adverse events including bleeding, ulceration, and perforation is noted in prescription NSAID class labeling.

This document provides a review of the safety and tolerability of naproxen sodium used at OTC doses. This safety review summarizes two large, published meta-analyses including a total of several thousand patients treated with naproxen or naproxen sodium in randomized, double blind, placebo-controlled clinical trials at OTC single doses and multiple doses up to 880 mg daily for ten days duration. The data from both large meta-analyses indicate that the frequency and severity of adverse events associated with

naproxen sodium, taken as directed, are similar to placebo. No deaths and no medically serious events occurred in any of these studies. Further, in studies with active controls, the overall rate of adverse events in the naproxen sodium groups did not exceed the rate of adverse events seen with ibuprofen or acetaminophen. In direct comparisons with acetaminophen, the only statistically significant difference was observed for vomiting, which occurred more frequently with acetaminophen.

The absolute risk of major upper GI bleeding from naproxen sodium at OTC doses is very low, estimated at 0.026 %. The large meta-analyses reported here documented no serious gastrointestinal events, and no statistically significant difference between active and placebo groups for any reported gastrointestinal event. Similarly, there were no serious renal events in these naproxen sodium OTC studies. Between 1995 and 2000 no fatal overdoses involving naproxen/naproxen sodium were reported by the American Association of Poison Control Centers. (The greatest number of fatal OTC analgesic overdoses during this period occurred with acetaminophen – 672 fatal overdoses.)

Consumers report high levels of satisfaction with the OTC options available for treatment of pain. The efficacy of naproxen sodium over the OTC dose range has been clearly demonstrated. Compared with other currently available OTC analgesics, naproxen sodium also provides consumers with the benefit of less frequent dosing. Given the broad market experience with naproxen sodium and its well-documented safety profile at OTC doses, the benefit of OTC availability of naproxen sodium outweighs the minimal risks associated with OTC use.

2 INTRODUCTION

It is Bayer's position that all of the analgesic/antipyretic drugs approved for OTC use are safe and effective when taken in accordance with labelling; nevertheless, there are differences in the pharmacology, efficacy, and adverse-event profiles of these drugs. Bayer appreciates the opportunity to participate in the discussion regarding the identification of risk factors for adverse events associated with the use of the OTC NSAIDs. We look forward to working with the Food and Drug Administration (FDA) and the Non-prescription Drugs Advisory Committee (NDAC) to consider any measures, if appropriate, that might effectively reduce the risk of occurrence of adverse events and better protect the consumer.

Since the introduction of aspirin, Bayer has been a research leader in the development of analgesic ingredients and has expanded its line of analgesic products. The Bayer product line includes naproxen sodium (Aleve®). Naproxen sodium was the subject of a New Drug Applications (NDA), which established its safety and efficacy based on a rigorous pre-marketing review of pre-clinical and clinical data. Naproxen sodium is a non-

steroidal anti-inflammatory drug (NSAID) used for a variety of pain disorders. In the United States, naproxen sodium is available as Aleve® for over-the-counter (OTC) use and as Anaprox® for prescription use. Anaprox has been available in the United States since 1980. After 14 years of prescription use, FDA approved naproxen sodium for OTC use under the trade name Aleve in 1994. Naproxen sodium together with aspirin, acetaminophen, ibuprofen, and ketoprofen are the only OTC agents approved by the US Food and Drug Administration (FDA) for the short-term treatment of pain, headache, dysmenorrhea, and fever.

This document reviews the safety and efficacy of naproxen sodium. The safety review includes summaries of two large, published meta-analyses including thousands of patients treated with naproxen or naproxen sodium at approved OTC doses in randomized, double blind, placebo-controlled clinical trials. This document review also includes a review of what is known about the occurrence of serious adverse events associated with NSAIDs, focusing on the categories gastrointestinal, renal, hepatic, and allergic. The efficacy review briefly summarizes the basis for the approved OTC dosing regimens, substantiating the basis for the minimum effective dose and approved dose range, and justification for the approved dosing interval, and justification for a loading dose.

The document closes with a brief review of Bayer's combination products containing naproxen sodium and a discussion of the overall risk-benefit of its OTC products containing naproxen sodium.

3 BAYER POSITION

The adverse event profiles of NSAIDs are well known, with the majority of the literature addressing NSAID toxicity at prescription doses. NSAIDs are known to have effects on the gastrointestinal, hepatic, and renal systems. NSAIDs may cause epigastric distress, nausea, and vomiting; in some cases they may also cause gastric ulceration, exacerbation of peptic ulcer symptoms, gastrointestinal hemorrhage, and erosive gastritis. NSAIDs are also known to have effects on the kidney, and the potential for renal toxicity is noted in prescription NSAID class labeling.

While serious adverse events may occur at prescription doses, data from randomized, controlled clinical trials for treatment of approved OTC indications at approved OTC doses in accordance with labeling, as presented in this document, demonstrate that naproxen and naproxen sodium are well tolerated and serious adverse events are extremely rare.

Nevertheless, data from the FDA Adverse Event Reporting System (AERS), recently made public, indicate that all of the OTC NSAIDs including naproxen have been associated with rare but serious GI events including hemorrhage, ulcer, or perforation; or with renal failure. Some of these patients with serious gastrointestinal events were affected by factors that have been identified to increase the risk of these events, such as age over 65, prior history of ulcer, and the use of high doses or duration (beyond OTC labeling) or multiple NSAIDs. The rare cases of renal failure occurred either as result of hypovolemia associated with gastrointestinal bleeding or vomiting or a result of direct renal hypersensitivity. Risk factors in these patients appeared to be excessive dose or duration of dosing, and a prior history of renal disease, hypertension, or use of diuretics.

Bayer is committed to do everything possible to ensure that its products are used safely to the benefit of the consumer. Accordingly, Bayer supports efforts by the FDA to identify patient risk factors that may be associated with use of OTC NSAIDs and consideration of measures that could be taken to reduce the risk of occurrence or decrease morbidity if an event should occur. Bayer also supports measures to encourage consumers to use these and all OTC products in accordance with approved labeling. These measures could include a variety of means, including changes to class labeling, intended to better educate and inform the consumer. Since each drug class represented among the approved OTC analgesic drugs has its characteristic pharmacology and adverse event profile, Bayer believes that changes to labeling that are identical across all analgesics are scientifically inaccurate and do not serve the public interest.

4 SAFETY AND EFFICACY OF OTC NAPROXEN SODIUM

As a prescription drug, naproxen in both its forms (i.e., naproxen free acid and naproxen sodium) has been widely used worldwide and has an extensive market history. Its safety and efficacy profiles have been well established over the course of more than 25 years of prescription availability.

OTC naproxen sodium (Aleve®) is indicated for the temporary relief of fever and minor aches and pains due to common cold, backache, headache, menstrual cramps, toothache, minor pain of arthritis, and muscular aches in adults and children 12 years of age and older. The approved dose of Aleve® is 220 mg (200 mg naproxen and 20 mg sodium). Consumers are instructed to take 220 mg of naproxen sodium (one tablet) every 8 to 12 hours while symptoms persist, while consumers with experience may take an initial dose of 440 mg (two tablets) followed by 220 mg 12 hours later. Total dosage is not to exceed three tablets in 24 hours in individuals 12 -65 years of age. The maximum OTC-labeled dosage for naproxen sodium is 660 mg/day for 10 days for pain. Patients older than 65 years of age should not take more than 220 mg every 12 hours unless directed to do so by a physician.

The safety and efficacy of naproxen sodium in an OTC setting has been evaluated to date in approximately 100 studies. These studies were designed to evaluate the use of OTC naproxen sodium for indications appropriate to nonprescription analgesics. These studies utilized of a wide range of pain models: dental extraction, dysmenorrhea, headache, arthritis, ankle sprains, sore muscle, myalgia, sore throat, and cold. In addition, pharmacokinetic, fever, and home use studies were also done.

5 OTC SAFETY

When assessing the safety profile of any analgesic/antipyretic, including naproxen sodium, it is necessary to differentiate between two distinct patterns of use: chronic administration (usually at higher prescription doses) and OTC patterns of use. Notably, much of the published safety data on NSAIDs is based on prescription use. While prescription NSAIDs are commonly used at higher doses over longer durations, most OTC analgesics are used for only a few days, typically at doses lower than those available by prescription. Therefore, adverse events associated with use of an OTC drug are likely to be less frequent and less serious than those associated with prescription use of the same drug.

5.1 Overall Adverse Event Profile

5.1.1 Published Data

To date, two meta-analyses have been published examining the safety profile of OTC naproxen sodium.

Although patients in clinical studies are selected based on certain inclusion and exclusion criteria (e.g., patients with NSAID allergy or acute ulcer disease are excluded from studies), clinical trials evaluating NSAIDs are indicative of the types of adverse events that may occur after a product is marketed. These exclusions are also reflected in the Aleve product labelling. Hence, these meta-analyses serve as a compendium of the large amount of data generated from clinical studies on OTC naproxen sodium and provide very useful safety data.

The first meta-analysis[1], published by DeArmond and colleagues in 1995, was based on 48 randomized, double-blind, placebo-controlled clinical studies conducted between May 1988 and June 1994. The purpose of this meta-analysis was to evaluate the safety of OTC naproxen sodium as compared to ibuprofen, acetaminophen, and placebo. A total of 59 available studies were reviewed at the time this meta-analysis was performed and

48 studies fulfilled the inclusion criteria (randomized, placebo-controlled, double-blind, with at least one treatment group receiving 187.5 to 400mg of naproxen or 220 or 440mg of naproxen sodium). These studies examined the use of OTC doses of naproxen sodium or equivalent amounts of naproxen under a variety of conditions appropriate for treatment with non-prescription analgesics, including dental pain, dysmenorrhea, minor pain of arthritis, headache, cold/sore throat, fever, and musculoskeletal pain.[xx]

Of the 48 studies, 27 were single-dose studies and 21 were multiple dose studies of one to ten days duration. Nineteen studies included ibuprofen and 9 studies included acetaminophen as active controls. A total of 8404 patients were included in the analyses of which 4138 patients received naproxen or naproxen sodium (3589 patients received naproxen 187.5 to 400 mg and 549 received naproxen sodium 220 to 440 mg), 1574 received ibuprofen (200 or 400 mg), 671 received acetaminophen (500 to 1000 mg), and 2423 received placebo. The age of the patients ranged from 14 to 86 years, and approximately 3% of patients were $\geq$ 65 years of age.

Safety data were collected by questioning patients at each clinic visit as to whether they had experienced any adverse events. In some studies, patients were also required to record adverse events in a diary.

Across all 48 studies, for both the naproxen/naproxen sodium and placebo-treated patients, 83% reported no adverse events. Few patients withdrew prematurely from the studies because of adverse events. The adverse-event termination rates for the placebo (0.62%) and naproxen/naproxen sodium groups (0.68%) did not differ significantly. The most commonly reported adverse events were headache (6.4% placebo, 4.8% naproxen/naproxen sodium), nausea (3.1% placebo, 3.4% naproxen/naproxen sodium), and somnolence (1.9% placebo, 2.7% naproxen/naproxen sodium).

In the 19 studies comparing placebo (n=1061), naproxen/naproxen sodium (n=1808), and ibuprofen (n=1574), there were no statistically significant differences in adverse event rates among the three treatment groups. In the nine studies that directly compared placebo (n=362), naproxen/naproxen sodium (n=692), and acetaminophen (n=671), the only statistically significant difference was observed for vomiting, which occurred more frequently in the acetaminophen group (4.5%) than in the naproxen/naproxen sodium group (2.2%) or the placebo group (2.5%).

This meta-analysis by DeArmond et al. clearly demonstrates the low frequency of occurrence of adverse events associated with OTC naproxen sodium when taken as directed. Overall, the results showed there were no differences in rates of adverse events in comparisons of naproxen sodium versus placebo, ibuprofen, or acetaminophen.

A more recent examination of the safety profile of OTC naproxen/naproxen sodium was published by Bansal and colleagues in 2001.[ii] The purpose of this meta-analysis was to evaluate the safety of various doses and dosage regimens of OTC naproxen sodium

compared to placebo. Studies that comprised this meta-analysis were selected from a pool of 90 studies, which included studies conducted in support of OTC approval, studies conducted after approval, and postmarketing surveillance. A total of 46 clinical studies including 7282 patients met all inclusion criteria (i.e., randomized, placebo controlled, double-blind, administered either 200 mg naproxen or 220 mg naproxen sodium in single, multiple, or PRN doses) and were included in the statistical analyses. The most common reasons for study exclusion were absence of a placebo control or administration of tablet strengths other than 200/220 mg.

Various doses and dosage regimens were analyzed separately and comprised daily doses ranging from 200/220 mg to 800/880 mg of naproxen/naproxen sodium, administered as single (220 mg) and multiple doses (up to 880 mg) in both fixed-regimen and PRN-dosing studies. Doses higher than the recommended OTC dose were included to review the overall safety of exposure to higher doses of naproxen sodium. Table 1 shows the adverse events reported by more than 1% of patients receiving either active drug or placebo.

Table 1

Adverse Event	Patients Receiving Active* n (%)	Patients Receiving Placebo n (%)	p-Value
Dizziness	93 (2.0%)	55 (2.1%)	0.869
Dyspepsia	86 (1.9%)	49 (1.8%)	0.958
Headache	227 (4.9%)	181 (6.8%)	0.001
Nausea	205 (4.4%)	128 (4.8%)	0.455
Somnolence	111 (2.4%)	41 (1.5%)	0.014
Vomiting	81 (1.8%)	64 (2.4%)	0.054

**Occurrence rate, based on a total of 4623 subjects assigned to active and 2659 subjects assigned to placebo.*

Headache, nausea, somnolence, dizziness, vomiting, and dyspepsia were among the most commonly reported adverse events. Of these adverse events, rates of headache and vomiting were significantly higher among subjects receiving placebo. Only the rate of somnolence was significantly higher among those subjects receiving naproxen/naproxen sodium.

In addition, the overall occurrences of moderate and severe adverse events with naproxen/naproxen sodium at single low dose (220 mg), single high dose (440 mg), multiple doses (up to 880 mg daily), and PRN doses were comparable to placebo with no statistically significant differences observed. Headache (2.6% active, 3.8% placebo), nausea (2.6% active, 2.6% placebo), and vomiting (1.3% active, 1.8% placebo) were the most commonly reported (occurring in more than 1% of subjects) moderate and severe adverse events. These findings show low occurrence of reported moderate and severe adverse events associated with OTC naproxen sodium and attest to its relatively good safety profile up to and including a 10-day dosing period.

One of the main disadvantages of NSAIDs is the occurrence of gastrointestinal side effects documented in the literature. However, it should be noted that the majority of literature reports are based upon prescription strength doses of NSAIDs and not OTC doses. Therefore, the occurrence of adverse events associated with the digestive system were also evaluated in this meta-analysis. This analysis showed that the occurrence of gastrointestinal adverse events with naproxen sodium and placebo at single low, multiple dose, and PRN doses were comparable, and there were no serious gastrointestinal adverse events (i.e., gastrointestinal bleed or perforation). At single high doses of naproxen sodium, the frequency of gastrointestinal complaints was significantly lower for naproxen sodium than placebo. Nausea (4.4% active, 4.8% placebo), dyspepsia (1.9% active, 1.8% placebo), and vomiting (1.8% active, 2.4% placebo) were the most common gastrointestinal adverse events reported. There was no statistically significant difference between active and placebo groups for any of the reported gastrointestinal adverse events.

These results confirm the low occurrence of gastrointestinal adverse events associated with naproxen sodium at doses of 220mg/day to 880mg/day.

These meta-analyses show low rates of adverse events with naproxen sodium when used at non-prescription doses as directed. The overall rate of adverse events in the naproxen sodium groups did not differ from placebo, ibuprofen, or acetaminophen. Notably, no deaths and no medically serious events occurred in any of these studies. These findings attest to the favorable safety profile of naproxen/naproxen sodium dosed up to and including a 10-day dosing period.

Furthermore, these meta-analyses are compelling in providing us with substantial safety data from well designed clinical studies. The conclusions of these meta-analyses are reflective of the true occurrence of adverse events associated with OTC naproxen sodium when taken as directed.

5.2 Serious Adverse Events

Adverse drug reactions associated with the use of NSAIDs can generally be grouped according to four categories: gastrointestinal (GI), renal, hepatic, and allergic.

5.2.1 Gastrointestinal

Nearly all NSAIDs have been reported to cause gastrointestinal complications. These effects, which can range from mild dyspepsia to the development of gastroduodenal ulcers, hemorrhage, and perforation, are believed to be due to inhibition of prostaglandin synthesis. However there are relatively few studies available that have evaluated the GI toxicity of OTC doses of NSAIDs.[iii]

Using a prescription database to approximate OTC dosing, Strom and colleagues compared naproxen sodium and ibuprofen with respect to the risk of gastrointestinal bleeding requiring hospitalisation. The authors reported an extremely low absolute risk of major upper GI bleeding with both naproxen sodium (26 of 101,318 patients, or 0.026%) and ibuprofen (33 of 277,601 patients, or 0.012%), and concluded that "there is little additional absolute risk posed by the use of low-dose naproxen sodium compared with low-dose ibuprofen."[iv]

The meta-analyses discussed above documented that no serious gastrointestinal events (e.g., gastrointestinal bleed or perforation) were observed in the studies conducted to support OTC use of naproxen sodium. The occurrence of gastrointestinal adverse events with naproxen/naproxen sodium and placebo at single low dose, multiple doses, and PRN doses were comparable. Nausea, dyspepsia, and vomiting were the most common gastrointestinal adverse events reported. There was no statistically significant difference between naproxen sodium and placebo groups for any of the reported gastrointestinal adverse events. These results confirm the low occurrence of gastrointestinal adverse events associated with naproxen/naproxen sodium at low (220 mg), high (440 mg), multiple (up to 880 mg), and PRN OTC doses.

5.2.2 Renal

The renal effects associated with NSAIDs are believed due to the effect of NSAIDs to inhibit prostaglandin synthesis. These effects are dose-related and are readily reversible upon withdrawal of the drug.[v]

The renal safety profile of naproxen sodium is consistent with other currently marketed NSAIDs with which it has been compared. Even at prescription doses, reports of adverse events involving the kidney have been rare with naproxen sodium. Consistent with the prescription experience, very few renal events were observed in naproxen sodium OTC studies, and there were no serious renal events.

In one study[vi], patients over the age of 55 years with mild to moderate renal insufficiency (creatinine clearance < 70 ml/min and/or serum creatinine level ≥ 1.3mg/dl) tolerated a two week course of naproxen at a dose of 750mg/day without compromising renal function. Patients with intrinsic renal disease were excluded. This study demonstrates that naproxen is well tolerated even in patients with mild to moderate renal insufficiency.

5.2.3 Hepatic

Drug-induced hepatotoxicity can range from minor, transient elevations in liver transaminase levels, to diffuse inflammation, focal cellular damage, or further to fulminant hepatitis and liver failure. NSAIDs rarely cause hepatic injury. In contrast to the known effects of prostaglandin inhibition on gastrointestinal and renal function, prostaglandin inhibition is not associated with liver injury.[vii] In fact, there is no consistent mechanism of liver injury associated with NSAIDs. In general, the rare cases of liver injury associated with non-aspirin NSAIDS, including naproxen sodium, are thought to be due to an idiosyncratic reaction (immunologic or metabolic) rather than an intrinsic toxicity of the agents.

Although the hepatic effects of the currently available analgesic/antipyretic agents available OTC have not been directly compared in controlled studies, available data suggest that acetaminophen presents the most common cause of drug-induced hepatotoxicity.[viii,ix]

It is well known that large or excessive doses of acetaminophen taken over a short time period may result in life-threatening hepatotoxicity. Intentional acetaminophen hepatotoxicity associated with suicidal behavior is the leading cause of acute liver failure in the United Kingdom, and an estimated 100,000 cases of intentional acetaminophen overdose are reported each year in the US.[x] Notably, the incidence of unintentional acetaminophen hepatotoxicity in patients receiving acetaminophen at therapeutic doses is rising; these cases are associated with a high fatality rate.[x] Risk factors associated with such unintentional overdose include chronic alcohol consumption and prolonged fasting.

On the other hand, even at prescription doses, naproxen has been implicated in very few cases of hepatic injury. Only one case of fulminant hepatic failure has been attributed to a prescription dose of naproxen. A role for naproxen has been suggested in a few instances of cholestatic jaundice.[xi]

Although elevations in liver enzymes have been reported in studies involving chronic administration (3 to 12 months) of NSAIDs, including naproxen, this finding rarely progresses to frank liver failure. The incidence of severe hepatotoxicity with prescription therapy has been reported as 2 per 100,000 patients for ibuprofen, 4 per 100,000 patients for naproxen, and 9 per 100,000 patients for ketoprofen.[xii]

Using Medicaid data, Carson and colleagues examined the association between prescription NSAID use and risk of acute hepatitis. None of the individual NSAIDs examined, including naproxen, were associated with a statistically significant increased risk of acute hepatitis.[xiii] Similarly, in their review of epidemiologic research on drug-induced acute liver injury, Garcia-Rodriguez and colleagues found acute liver injury associated with prescription use of non-aspirin NSAIDs, including naproxen, to be rare, with a crude incidence rate ranging from 1.0-3.7/100,000 users.[xiv]

5.2.4 Allergy

Allergic reactions, ranging from minor localized rashes and urticaria to more serious systemic events such as anaphylaxis, have been reported with virtually all NSAIDs. Anaphylaxis or anaphylactoid reactions are a subset of a broader category that may represent the most potentially severe or life-threatening events with NSAIDs. Prescription NSAIDs are contraindicated in patients who have had allergic reactions to them or in whom aspirin or other NSAIDs have induced the syndrome of asthma, rhinitis, and nasal polyps. Current Aleve® labelling features a prominent warning that naproxen sodium may cause a severe allergic reaction that may include hives, facial swelling, asthma (wheezing), and shock. Consumers are also advised in the labelling not to use the product if they have ever had an allergic reaction to any other pain reliever/fever reducer, and are instructed to seek medical help immediately if an allergic reaction occurs. A similar warning currently appears on the label of ibuprofen-containing products.

Available data from population-based epidemiologic studies indicate that naproxen sodium is no more likely than other NSAIDs to induce hypersensitivity reactions, including anaphylaxis.

Using a large, computerized database derived from Medicaid claims, Strom and colleagues evaluated the risk of allergic reactions and/or anaphylaxis associated with the use of prescription NSAIDs, including fenoprofen, ibuprofen, indomethacin, naproxen, phenylbutazone, sulindac, tolmetin, and zomepirac.[xv] There was no overall difference in the incidence of hypersensitivity reactions among the NSAIDs. No hypersensitivity reactions were observed among 1,317 patients prescribed naproxen.

Using an on-line computerized Medicaid pharmaceutical analysis and surveillance system, Strom and colleagues conducted a 2-phase retrospective cohort study in Michigan, Minnesota, and Missouri to assess the relative risk of hypersensitivity reactions (allergic reactions and anaphylaxis) to six prescription NSAIDs (tolmetin, fenoprofen, meclofenamate, naproxen, prioxicam, and sulindac).[xvi] Of the 128,344 study subjects who were users of one of the 6 NSAIDs, the incidence rates per 10,000 patient use months were determined. The incidence rates are displayed by state for each of the six NSAIDs in Table 2.

Table 2

Drug	Incidence Rate (per 10,000 Patient-months): Michigan	Incidence Rate (per 10,000 Patient-months): Minnesota	Incidence Rate (per 10,000 Patient-months): Missouri
Fenoprofen	15.5	6.2	6.1
Meclofenamate	15.9	12.5	0
Naproxen	10.1	2.7	6.1
Piroxicam	12.0	2.4	0
Sulindac	7.7	4.5	0
Tolmetin	11.8	1.8	4.3

In a population based case-cohort study of drug-induced anaphylaxis for all admissions to hospitals in the Netherlands in 1987 and 1988, admissions were classified as to the possibility or probability of anaphylaxis by a blinded audit committee.[xvii] The causative agent was assessed for each case by chart review and dispensing data from 28 pharmacies in the area. From a total of 252 admissions for anaphylaxis during those 2 years, only 2 patients were judged to have reacted possibly to naproxen. For a number of admissions, the most common offending drugs were glafenine (20), amoxicillin (12), diclofenac (8), and acetaminophen (7). Thus, there was no evidence in this study that the rate of anaphylaxis to naproxen was higher than other NSAIDs.

A study conducted by McMahon and colleagues[xviii] evaluated the risks of hospitalization and death due to the hypersensitivity reactions associated with naproxen and ibuprofen using a database in Tayside, Scotland. There were 54,038 patients exposed to naproxen and 79,513 exposed to ibuprofen. There were no deaths due to hypersensitivity. There was an apparent increased risk of hypersensitivity reactions during periods on-drug versus off-drug in patients exposed to naproxen and ibuprofen. However, after checking medical records, none of the three valid cases of

hypersensitivity in the naproxen cohort and neither of the two in the ibuprofen cohort were judged to be due to NSAID exposure. The main finding of this study was that hypersensitivity reactions associated with NSAID use are rare and that the risks of hypersensitivity reactions associated with naproxen and ibuprofen do not differ.

5.2.5 Overdose

When examining the OTC use of any medication, the risk of accidental or intentional overdose is an important concern. Overdosing with naproxen sodium is typically characterized by drowsiness, heartburn, indigestion, nausea, and/or vomiting. Between 1995 and 2000, no fatal overdoses involving naproxen/naproxen sodium were reported by the American Association of Poison Control Centers. The greatest number of fatal overdoses from an OTC analgesic during this time period occurred with acetaminophen (672 fatal overdoses).

5.2.6 Experience Outside the U.S.

Naproxen sodium is approved and marketed at a dose of 220mg in the following countries: Argentina, Australia, Belgium, France, Germany, Italy, Netherlands, New Zealand, Poland, South Africa, and Switzerland.

5.3 Safety Conclusions

The safety of prescription doses of naproxen sodium has been well established as prescription naproxen sodium has been available for more than 20 years in the United States. The broad experience with naproxen sodium in studies conducted specifically to support OTC use indicate that naproxen sodium, at the dosages studied, is a safe OTC analgesic. The rate and severity of adverse events associated with naproxen were similar to those associated with placebo as concluded in two large meta-analyses detailed above. For the range of doses studied (up to 880 mg/day), no overall dose-related increase in adverse events was evident. Available data indicate that naproxen sodium represents a safe OTC analgesic that compares favorably to other analgesics available on the market.

6 EFFICACY

Naproxen sodium, the sodium salt of naproxen, was developed as an OTC analgesic because it is more rapidly absorbed than naproxen. Naproxen sodium is an effective NSAID used for a variety of pain disorders. Prescription strength naproxen sodium is typically used for chronic conditions on a long-term basis, whereas OTC naproxen sodium is used for acute conditions for no more than 10 days. The dose of OTC naproxen sodium is 220 mg, and its approval was supported by more than 20 years of experience with prescription strength naproxen sodium. The safety and efficacy of naproxen sodium in an OTC setting has been evaluated in approximately 100 studies to date.

6.1 Minimum effective dose

The NDA[xix] for Aleve® was approved by the FDA in 1994. Overall, results from the clinical program demonstrated 220 mg of naproxen sodium to be the lowest effective dose for OTC pain conditions. The evidence from dental, dysmenorrhea, headache, osteoarthritis, sore muscle, and cold studies clearly support this dosage regimen. Some studies demonstrated that a dose substantially lower than 220 mg of naproxen sodium did not provide adequate pain relief for patients.

6.2 Justification for loading dose

Due to inter-individual variability in pharmacokinetics and the concentration-response relationship, some patients will not achieve adequate analgesia with the first dose and will require a second dose within the first hour after dosing. Based on PK/PD simulations, analgesic effect after a second dose is expected to last significantly longer than after a single dose because of this loading effect.

Dysmenorrhea and dental studies have suggested that a better analgesic effect could be achieved in some patients with a higher (two-tablet) initial dose. In addition, it was found that patients who started with 440 mg naproxen sodium as the initial dose waited longer before re-medicating compared with those who started with an initial dose of 220 mg of naproxen sodium. Therefore it was deemed beneficial for patients to be given the option of taking an initial dose of one (220 mg) or two (440 mg) tablets of naproxen sodium.

6.3 Justification for Dosing Interval

Naproxen sodium's plasma half-life is approximately 13 hours, whereas the half-lives of aspirin, acetaminophen and ibuprofen are 3.2 hours or less. This longer half-life allows for less frequent dosing (every 8-12 hours) with naproxen sodium compared with other OTC analgesics, for which the dosing regimen is typically every 4 to 6 hours.

The data submitted in the NDA for Aleve® support a dosing interval of 8 to 12 hours following the initial dose.

6.4 Efficacy Conclusions

In summary, the safety and efficacy of naproxen sodium in an OTC setting has been evaluated in approximately 100 studies to date. These studies have provided evidence of naproxen sodium's therapeutic benefit and safety as an analgesic for OTC use.

In summary, as a prescription drug, naproxen in both its forms (i.e., naproxen free acid and naproxen sodium) has been widely used worldwide and has an extensive market history. Its safety and efficacy profiles have been well established over the course of more than 25 years of prescription availability.

Doses of 220 mg and higher were demonstrated to be efficacious for various pain states as: dental pain, headache, muscular aches, backache, menstrual cramps, minor pain of arthritis, and minor aches and pains due to the common cold. On the basis of the data submitted in the NDA for Aleve®, FDA concluded in 1994 that naproxen sodium, at a dosage of 220 mg, is a safe and effective analgesic/antipyretic agent for OTC use.

7 NAPROXEN SODIUM COMBINATION PRODUCTS

Many of the OTC analgesics available today are included as one of several active ingredients in numerous cold, allergy, and/or sinus products. For example, there are more than 200 OTC products available that contain acetaminophen.[x] There are however, only two combination products currently marketed that contain naproxen sodium. These products are Aleve® Cold & Sinus and Aleve Sinus and Headache.

In January 1999, the Consumer Care Division of Bayer Corporation submitted an NDA to the FDA in support of the OTC availability of a combination naproxen sodium (220 mg)/pseudoephedrine hydrochloride (120 mg) product for the temporary relief of cold, sinus, and flu symptoms.[xx] Pseudoephedrine hydrochloride is recognized by OTC

monograph as a safe and effective nasal decongestant in adult doses up to 240 mg/day and was available in a number of OTC cold, allergy, and/or sinus products.

In November 1999, FDA concluded that the combination product was safe and effective for OTC use.

Aleve® Cold & Sinus and Aleve® Sinus & Headache are both indicated for the temporary relief of the cold, sinus and flu symptoms of sinus pressure, minor body aches and pains, headache, nasal and sinus congestion and fever in adults and children 12 years of age and older. Consumers are instructed to take one caplet every 12 hours. Total dosage is not to exceed two caplets in 24 hours.

Both naproxen sodium and pseudoephedrine have been judged by the medical community and the FDA as safe and effective for OTC use. These drugs have acceptable safety profiles supported over the past 25 years by extensive clinical studies and post-marketing surveillance. For people with cold or flu who need both an analgesic/antipyretic and a nasal decongestant, the combination provides the convenience of twice-a-day dosing.

Given the limited availability of OTC combination products containing naproxen sodium, and the modest amount of use with the combination product compared to the total use of naproxen sodium alone, the likelihood is low that consumers are unknowingly exposed to naproxen sodium in excess of recommended doses.

8 BENEFITS AND RISKS

Over the past several years, consumers have become increasingly interested in and have recognized the importance of self-care. The availability OTC medications plays a vital role in the ability of consumers to take responsibility for their own health. These medications provide consumers with ready access to effective relief for a broad range of medical conditions.

Of the many different health conditions routinely experienced by consumers, pain is one of the most common. Forty-eight percent of respondents to a recent consumer survey reported that they experienced muscle, back, or joint pain at some time within the preceding 6 months. Along with cold and cough, this was the most common health condition reported by respondents.[xxi] Similarly, forty-three percent of those responding to the same survey reported experiencing a headache within the past six months. Such pain can have an important impact on the lives of sufferers, often affecting appetite and sleep, and interfering with normal activities.

Various surveys and studies have demonstrated that consumers rely on OTC medications more than any other treatment approach when searching for pain relief. In fact, the most common ailment for which Americans take OTC medicine is for pain: 78% of those who have taken a nonprescription medication in the past six months have done so to relieve pain.[xxii] Among all of the FDA-approved drugs available in the U.S., taken either as single- or multiple-component products, acetaminophen, ibuprofen, and aspirin are the three most commonly used, with use in the preceding week reported by 23%, 17%, and 17% of U.S. adults, respectively.[xxiii] Naproxen is the twelfth most frequently used drug, with use in the preceding week reported by 3.5% of adults.

Consumers report high levels of satisfaction with the OTC options available for the treatment of pain. Among those who have experienced a headache in the past six months, 92% report being satisfied with how well their OTC medication relieved them of their pain and suffering. Similarly, among those who report experiencing muscle, joint, or back pain in the past six months, 89% report being satisfied with the OTC medication they used to treat their pain.[xxi]

OTC medications are the preferred means of treating many minor ailments and conditions, particularly pain. Given that pain is one of the most frequently and costly health conditions, providing consumers with access to safe and effective OTC medications becomes an important and integral part of the health care system.

Naproxen sodium represents a valuable OTC alternative for consumers. It provides a safe and effective alternative to other existing OTC analgesics.

As is the case with other NSAIDs, the most frequent adverse events observed in clinical trials with OTC use of naproxen/naproxen sodium are associated with the gastrointestinal (i.e., nausea, dyspepsia) or nervous systems (i.e., headache, somnolence, dizziness). Results from clinical studies indicate that these digestive and nervous system events occur with the same or lower frequency in the naproxen groups as compared to the placebo groups. Other adverse events are similar to those observed with other OTC analgesic products. Compared with other currently available OTC analgesics, naproxen sodium also provides consumers with the benefit of less frequent dosing. The benefits of OTC availability of naproxen sodium far outweigh the minimal risks associated with its use.

9 CONCLUSIONS

Naproxen sodium is a safe and effective alternative to other existing OTC analgesics and provides the benefit of less frequent dosing.

There is extensive and substantial evidence of the safety and efficacy of naproxen sodium, at the recommended dosages, as an OTC analgesic/antipyretic agent. This evidence is based on more than 25 years of prescription availability, data from approximately 100 clinical studies conducted specifically to support OTC use to date, and data available in the published literature.

In 1994, FDA approved naproxen sodium at a dose of 220mg for OTC use in the United States based on the data submitted in NDA #20-204. All data since the FDA approval continue to support the safety and efficacy of OTC naproxen sodium.

Available data support the following:

- The rate and severity of adverse events associated with naproxen/naproxen sodium at OTC doses are similar to those associated with placebo;
- There is a low occurrence of gastrointestinal adverse events associated with naproxen sodium at low (220 mg), high (440 mg), and multiple (up to 880mg/day) OTC doses;
- Naproxen/naproxen sodium is relatively safe and well tolerated;
- Hepatic events related to naproxen sodium use are extremely rare;
- The risk of anaphylaxis due to naproxen sodium use appears to be no different from that associated with the use of other NSAIDs;
- No health hazards are associated with the amount of sodium provided by OTC naproxen sodium;
- The minimum effective dose of naproxen sodium (220 mg) is clearly substantiated with extensive and well researched clinical data;
- Better analgesic effect may be achieved in some patients and in some indications with a higher (two-tablet) initial dose;
- A dosing interval of 8 to 12 hours following the initial dose is appropriate and well substantiated;

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